POLITÉCNICA

"We engineer the future"

Department of
Electronic Engineering

Image processing methods for human brain connectivity analysis from in-vivo diffusion MRI

Ph.D. Thesis

Esteban Sanz-Dranguet, Oscar

Biomedical Image Technologies (BIT),
Dept. Ing. Electrónica
ETSI Telecomunicación, Universidad Politécnica de Madrid
Advisors: Andrés Santos and María-J Ledesma-Carbayo

November 25th, 2015

As humans, we can identify galaxies light years away and we can study particles smaller than an atom, but we still haven't unlocked the mystery of the 3 lbs. of matter that sits between our ears.

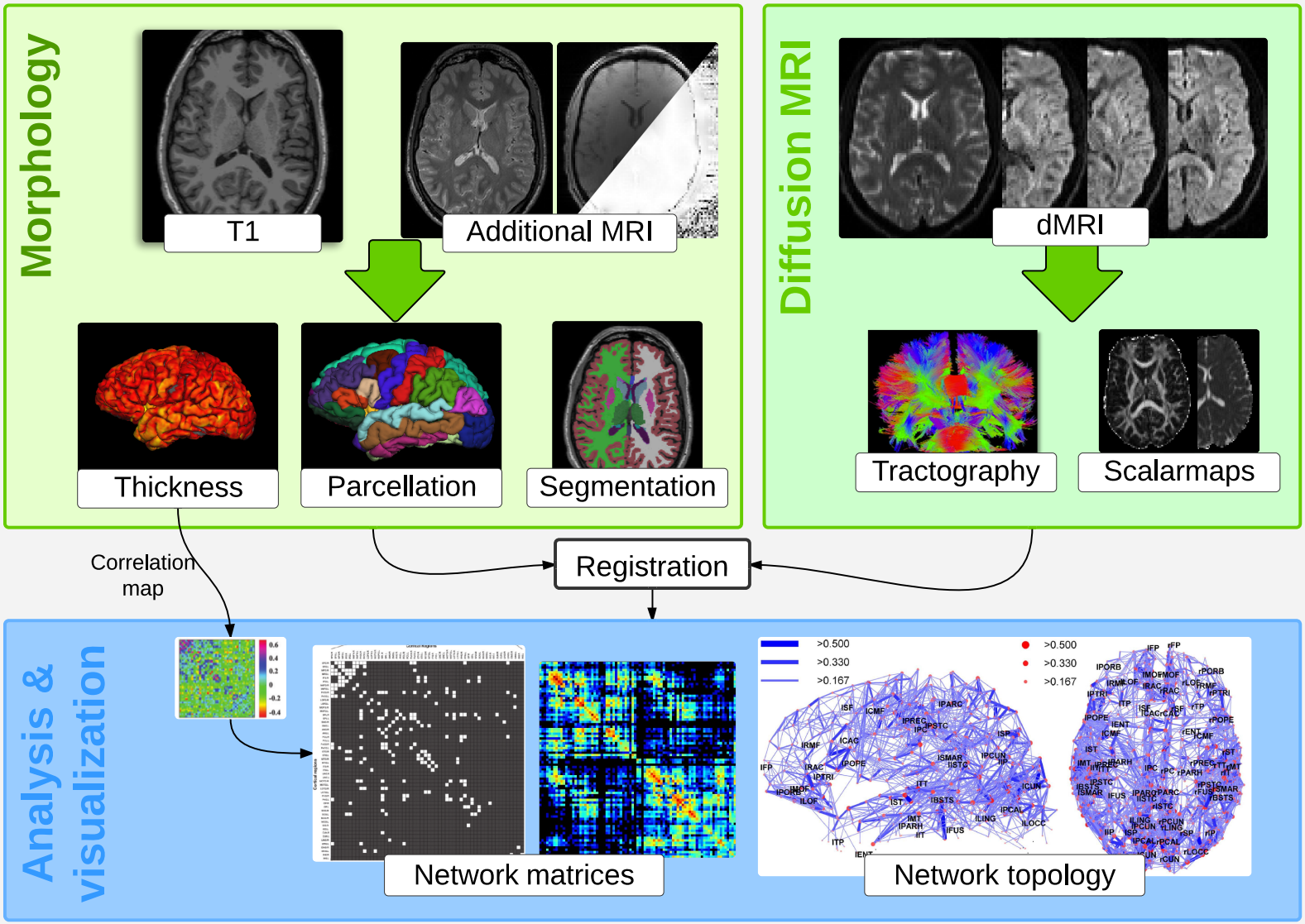
Barack Obama, President of the United States, April 2013

Table of Contents

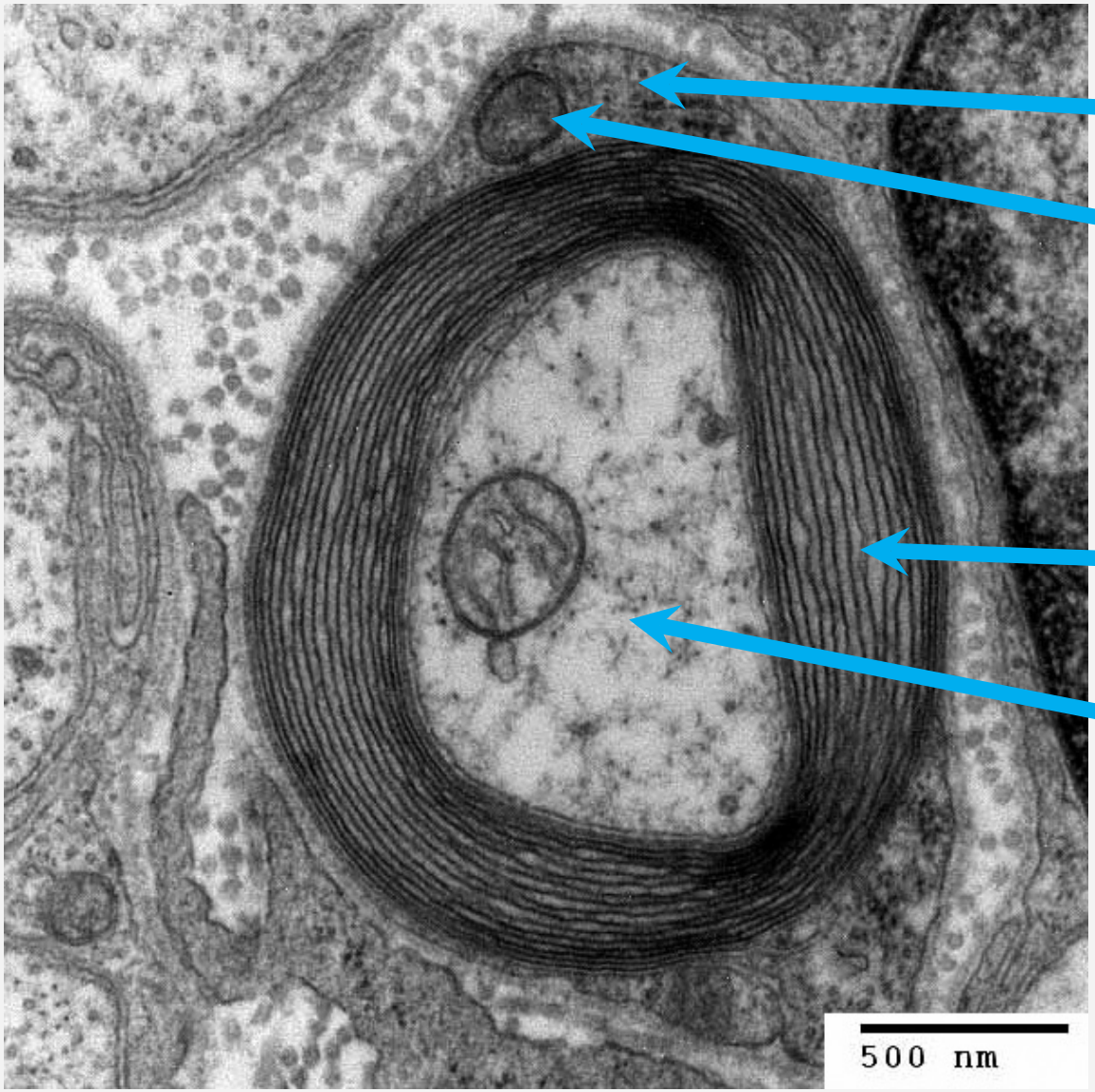
Context: the human connectome mapping

- The human brain is the organ system least known.
- In 2005 starts the quest of mapping the ***human connectome***, the individual fingerprint of the "wiring" connecting regions of the brain.
- Expected to unveil ***new biomarkers*** for research (Sporns, 2012) and clinical application (Griffa et al., 2013).
- Enabling technology to map it ***in-vivo***: diffusion MRI (dMRI, Le Bihan and Breton, 1985).
- Large funding initiatives: Human Brain Project (EU), BRAIN (US), etc.

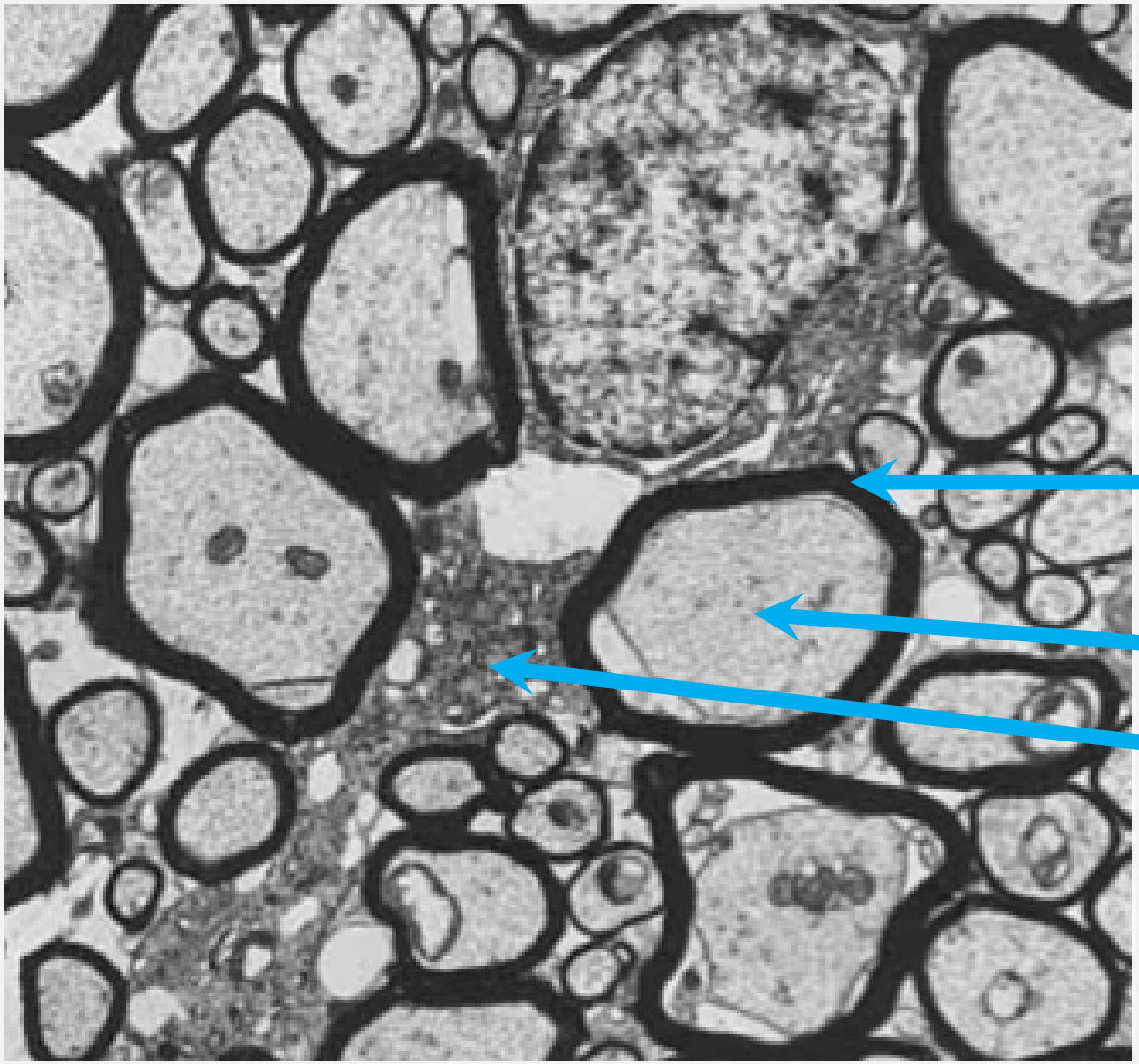
Overview of the connectome extraction processing flow



Why/How it works?: microstructure of tissues

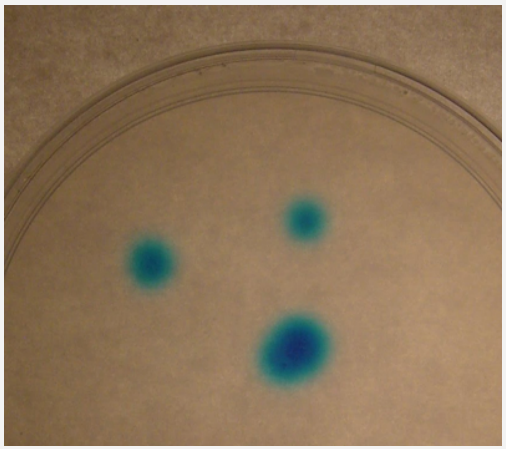


Why/How it works?: microstructure of tissues



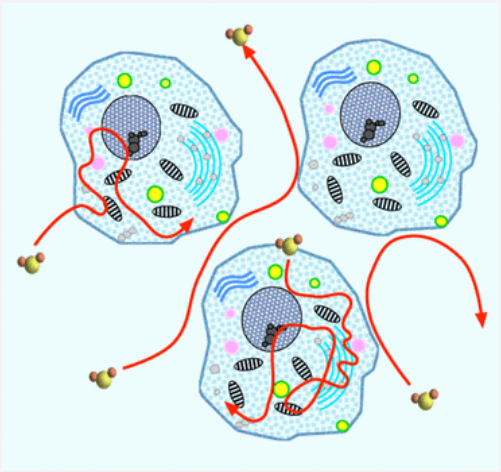
Why/How it works?: microstructure of tissues

CSF (cerebrospinal fluid)



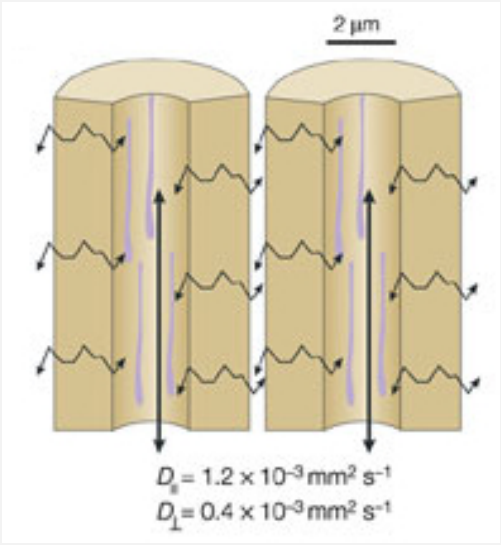
Free diffusion (only extracellular)

GM (grey matter)



Hindered diffusion (intra-, extra- and exchange)

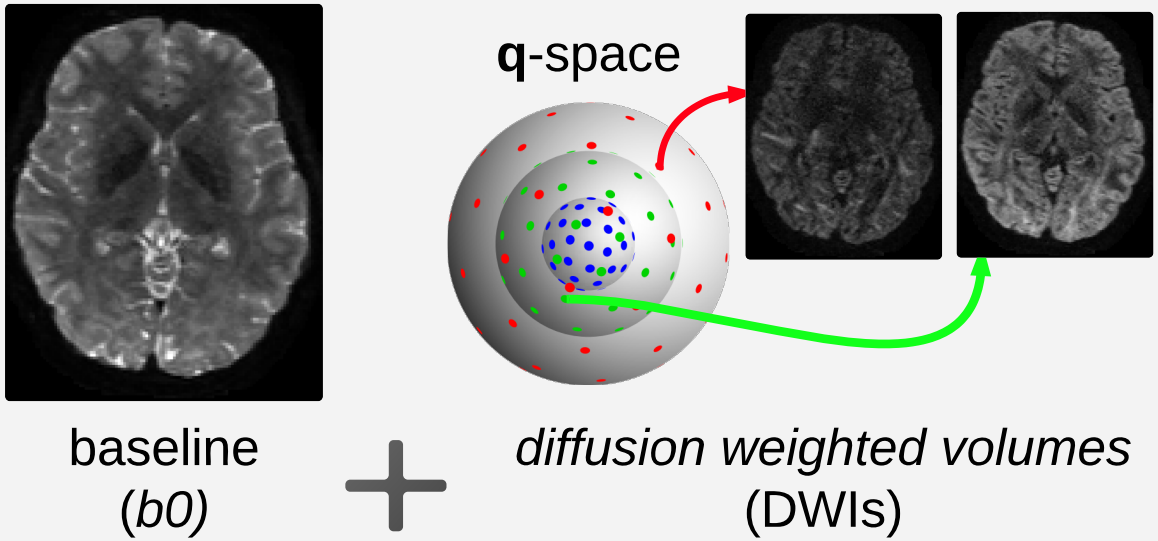
WM (white matter)



Restricted diffusion (confined in the axial orientation)

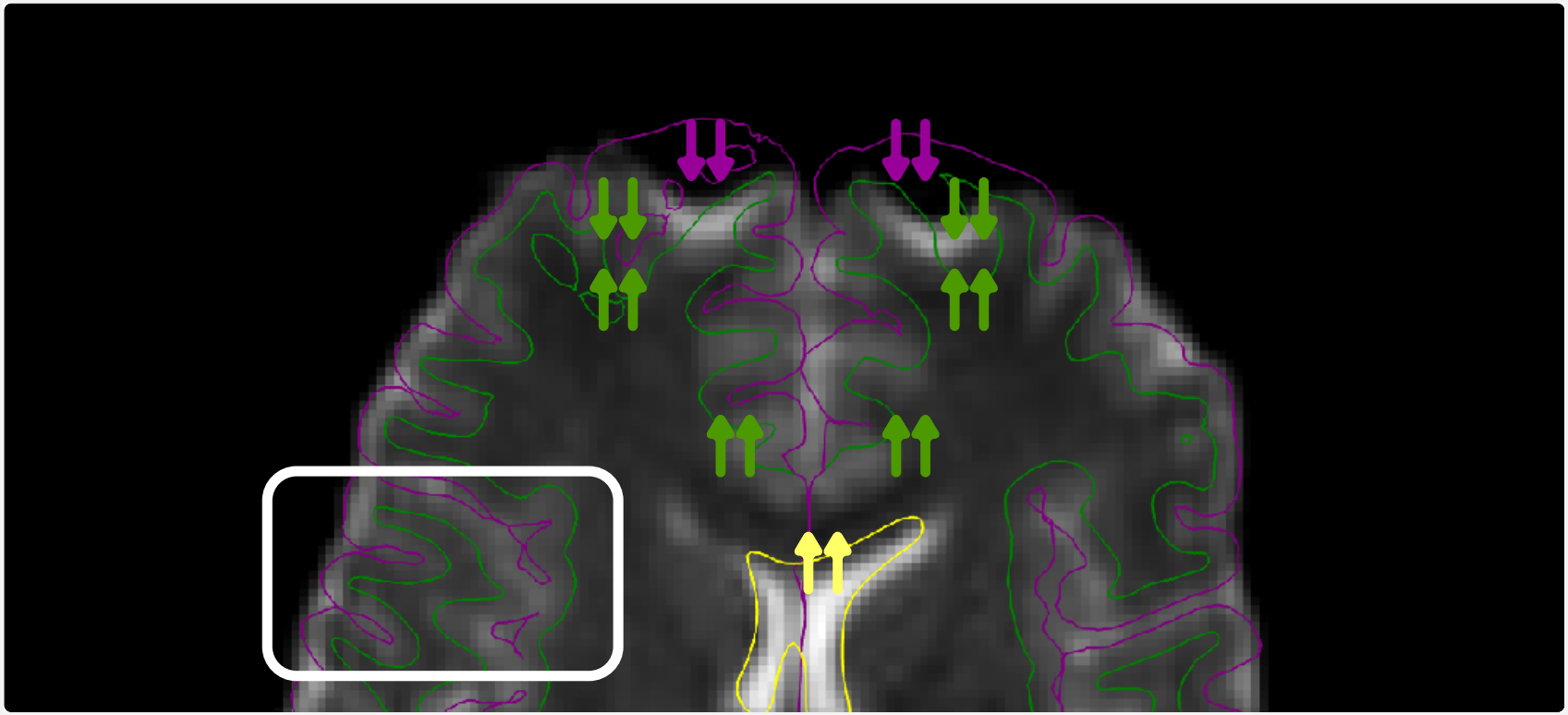
- Components of diffusion in the white-matter (WM): intracellular diffusion, extracellular diffusion and exchange between intra- and extra-cellular space.

Scanning the diffusion weighted volumes (DWIs)



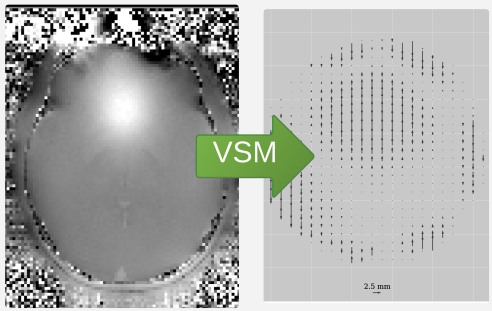
- The faster diffusion is in the sampled orientation (in the $\mathbf{q}$-space) and voxel, the lesser signal registered in that voxel and DWI volume.
- Then, a model of diffusion orientation is fitted.
- The simplest model is **DTI** (Basser and Pierpaoli, 1996). It needs at least 6 DWIs. Generally: 32, or even more DWIs.

The origin of the problem: EPI distortion

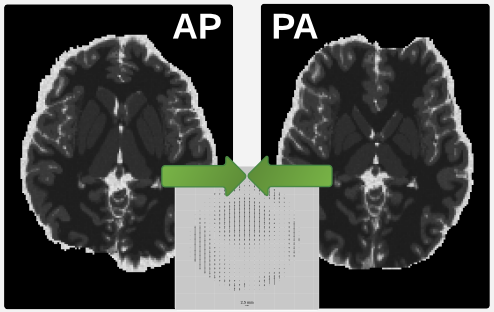


- dMRI is acquired with Echo-Planar Imaging (EPI).
- EPI is very fast, but introduces nonlinear distortion aligned with the phase-encoding (PE) direction.
- Magnitude of warping $\propto$ inhomogeneity of field (B_0).

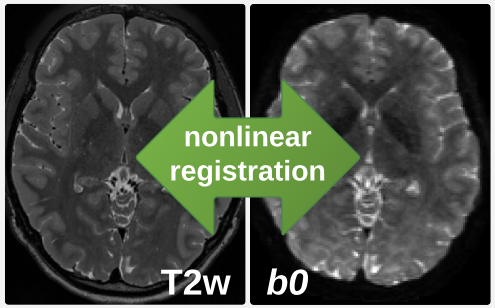
Option A: Susceptibility Distortion Correction (SDC) methods



FMB (Jezzard and Balaban, 1995)



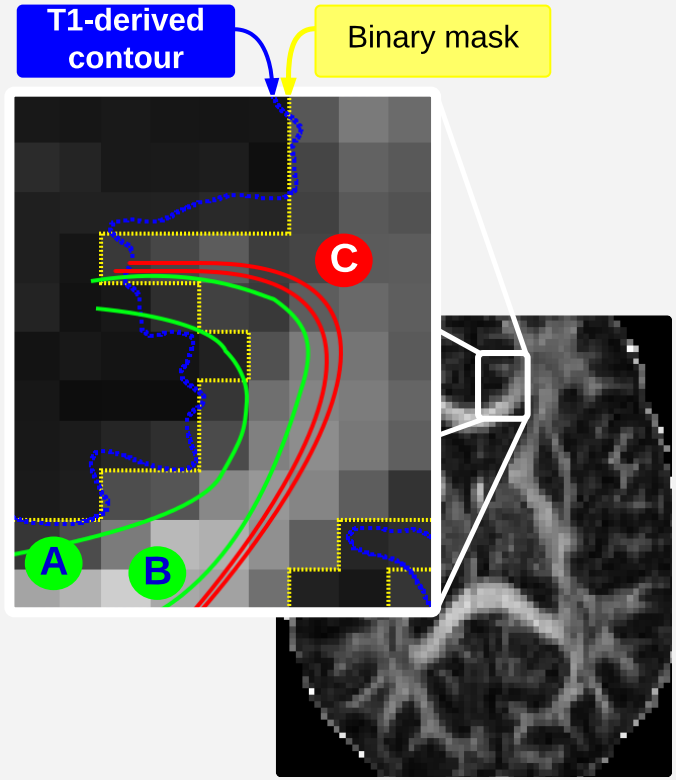
rPEB (Chiou and Nalcioglu, 2000)

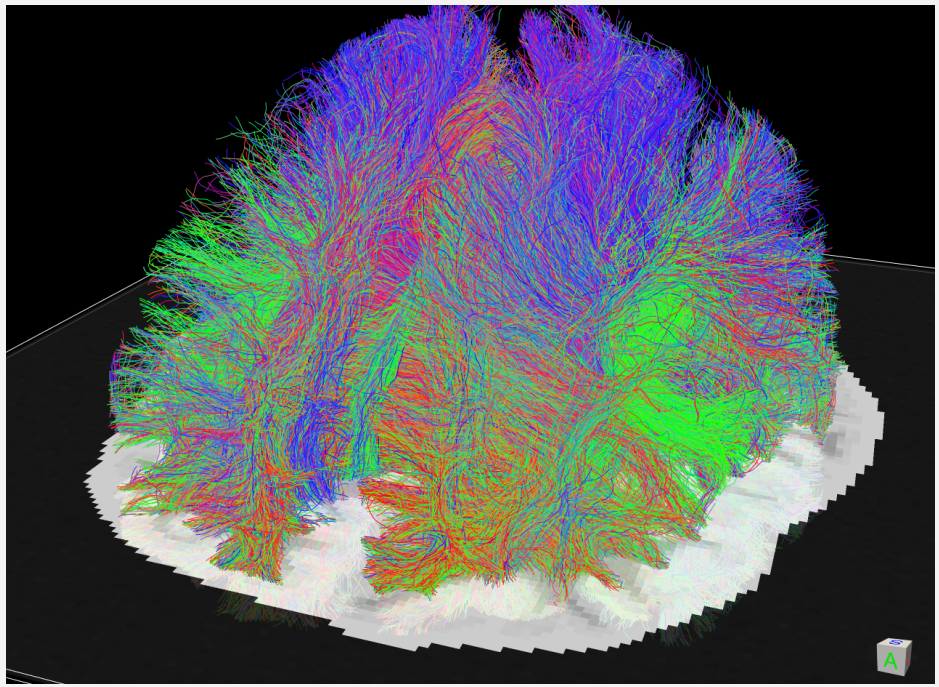


T2B (Kybic et al., 2000)

- All look for the underlying deformation field. The field is **nonzero only in the component of PE**.
- All need for **additional acquisitions**.
- Alternatives (Robson, Gore, and Constable, 1997), and many improvements (Irfanoglu et al., 2015).
- Retrospective correction requires resampling of DWIs with **unknown consequences**.

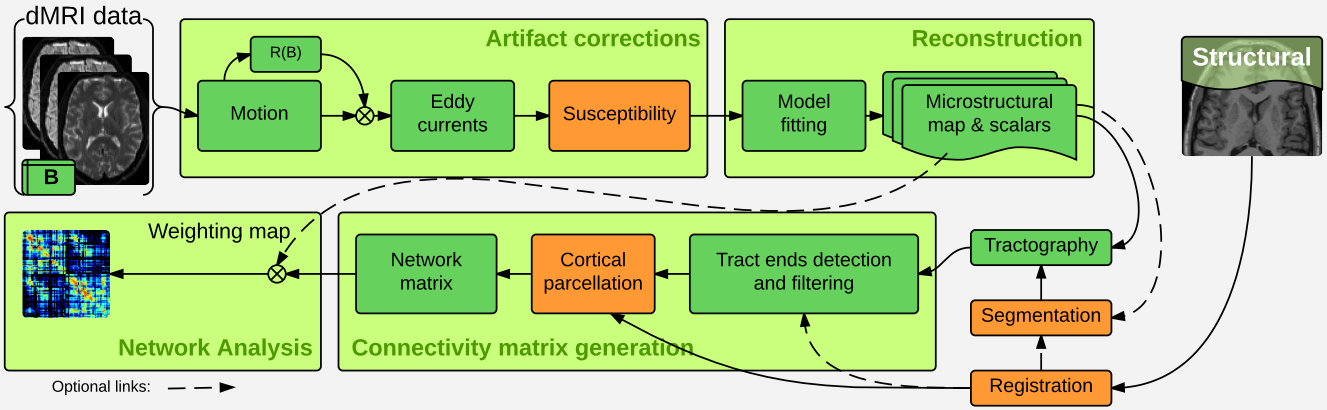
Option B: Image segmentation in native (dMRI) -space





- Early: WM-mask (FA thresholding) for termination criterium.
- Numerous segmentation methods have been proposed, without suitable results (noise, low resolution of dMRI, etc.).

Motivation



- Established connectome extraction pipelines are complex, and **unreliable** (Buchanan et al., 2014).
- Existing **validations are limited**:
  - **missing gold standards** and ground-truth datasets,
  - only test modules, with very **specific** benchmarks (e.g. accuracy),
  - many are **qualitative** (visual),
  - concerns with **data quality** (Lauzon et al., 2013).
- Model fitting (Jeurissen et al., 2014) and tractography (Smith et al., 2012) are **increasingly using structural information** (perform segmentation and registration earlier).

Objectives

General: **the characterization of the *susceptibility distortions*, the evaluation of existing correction methods and proposing alternatives** in the context of the connectome extraction.

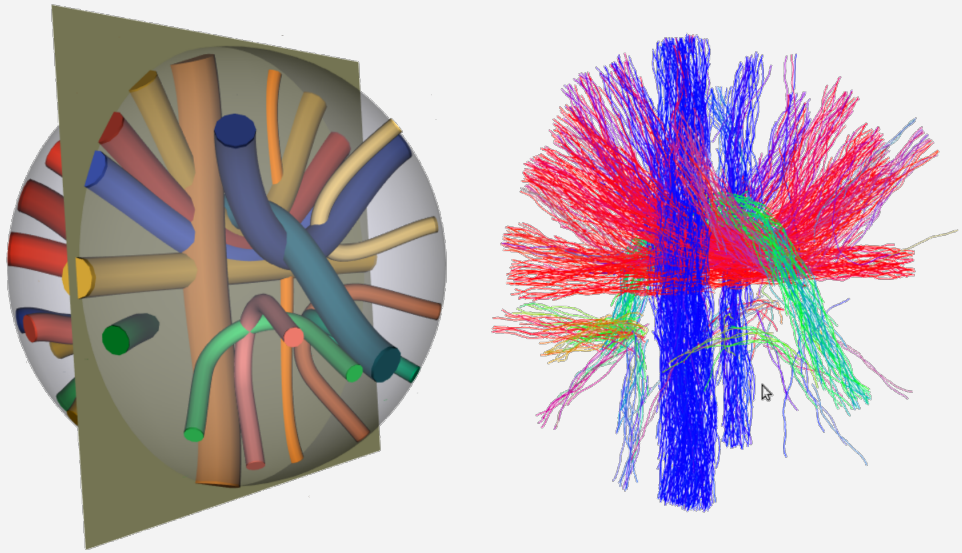
Specific:

- A **comprehensive verification and validation framework** for connectivity pipelines.
- A **characterization of the susceptibility-derived distortions and their impact on whole-brain networks**.
- A **simultaneous registration and segmentation method** for dMRI data.

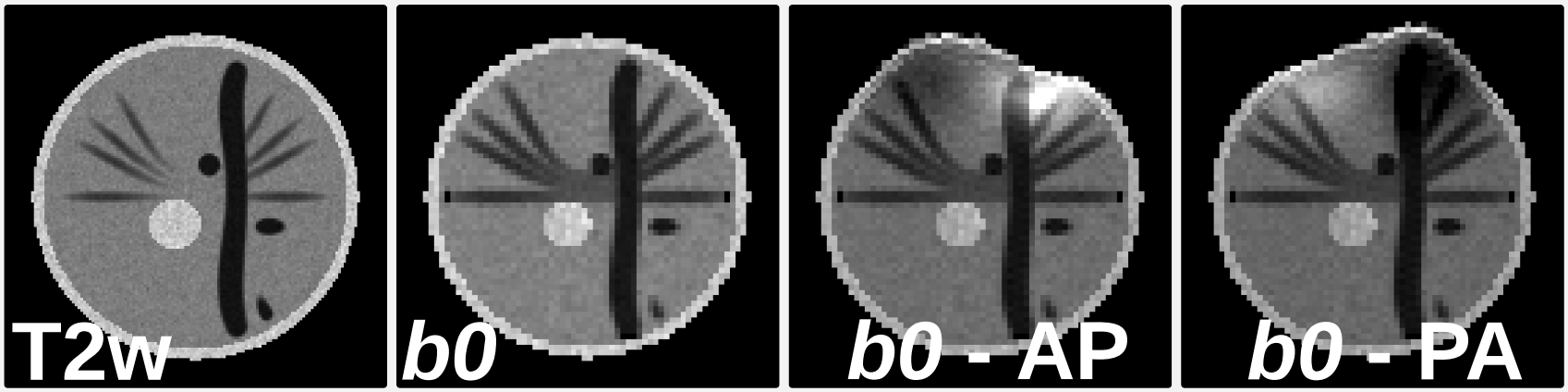
Hypothesis: distortions and SDCs have an important impact on connectivity analyses, oftentimes underestimated.

Gold standards: Phantomas

- 27 fiber bundles
- $70 \times 70 \times 70$ (voxels)
- $1.0 \times 1.0 \times 1.0$ (mm).
- Default: 64 DWIs (b=3000s/mm^2).
- Customizable $\mathbf{q}$-space sampling.
- 3695 voxels of pure WM
- 1192 voxels >1 fiber bundles.
- HARDI Challenge, ISBI 2013.
- Caruyer et al., 2014.

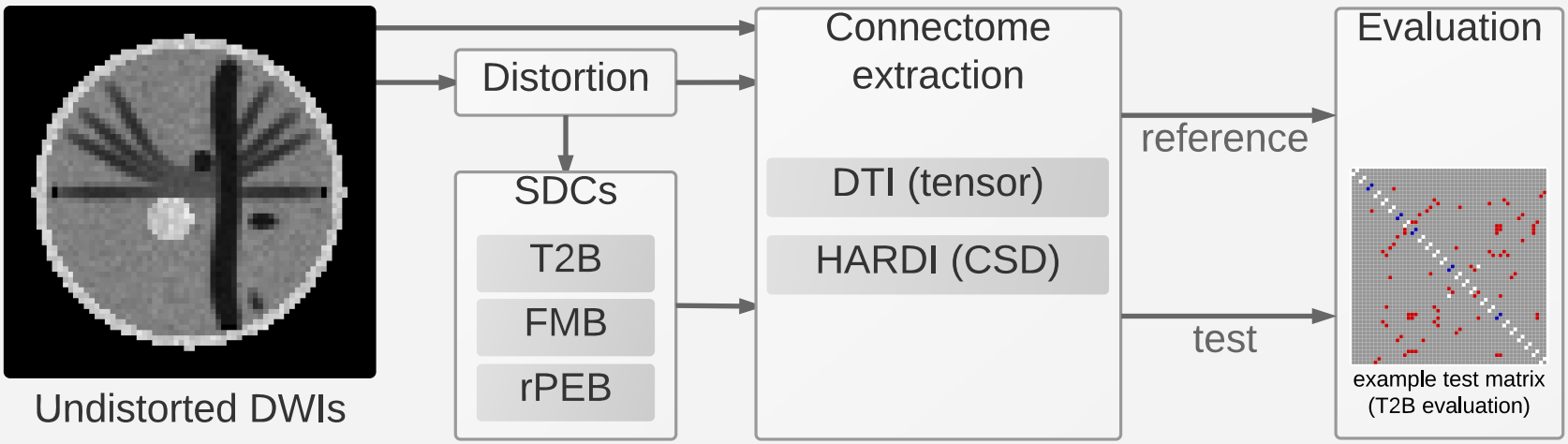


- Testing susceptibility distortions:



Experiment 1: methods

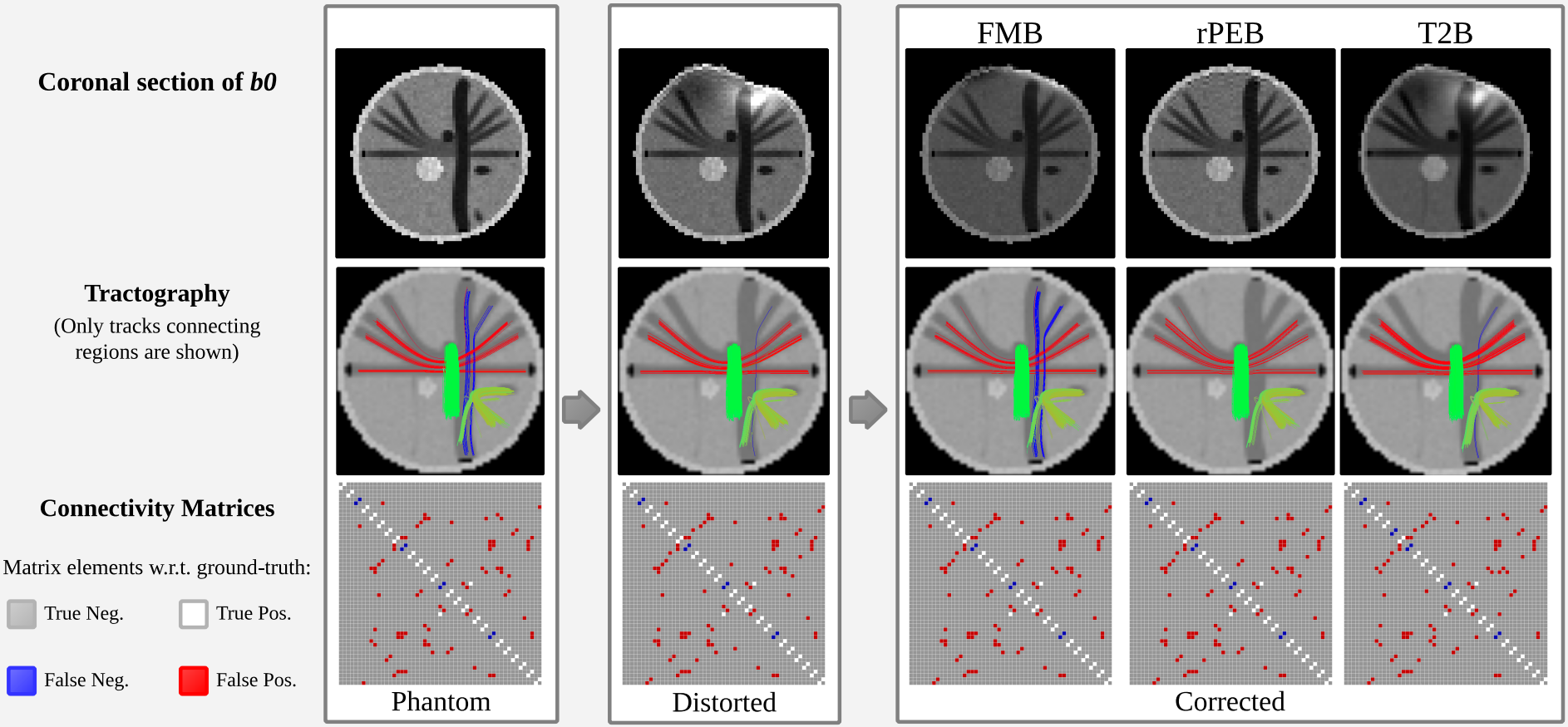
- 2 versions of *Phantomas*: 32 DWIs for DTI & 64 DWIs for HARDI.
- Comparing 3 SDCs: FMB, rPEB, and T2B.
- Distortion range $\max|\Delta y| =$ (3.80–7.60) mm.



- Early conclusion: DTI unsuitable for reconstructing *Phantomas*.

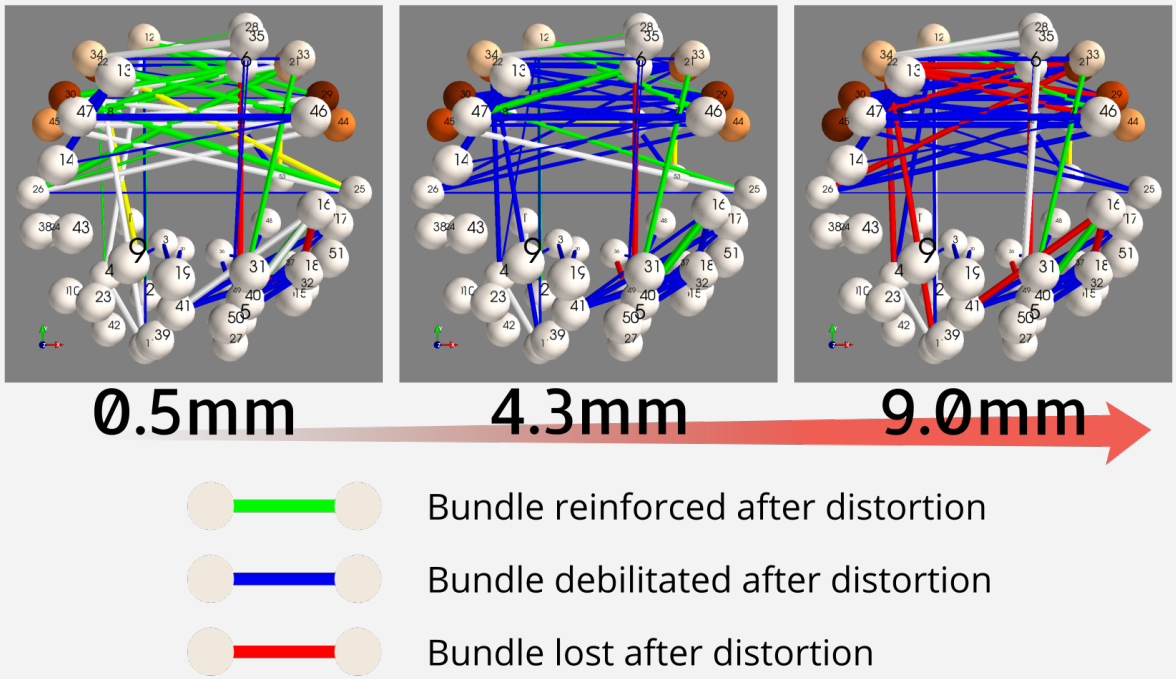
Experiment 1: results

- All SDCs under test improved detection.



Experiment 2: methods & results

- Only tested impact of distortion
- Wider distortion range, $\max|\Delta y| =$ (0.5–9.0) mm.
- **Networks change importantly** even with very small distortions.
- 27 connections ($+$ 40 false positives) is **not enough**.

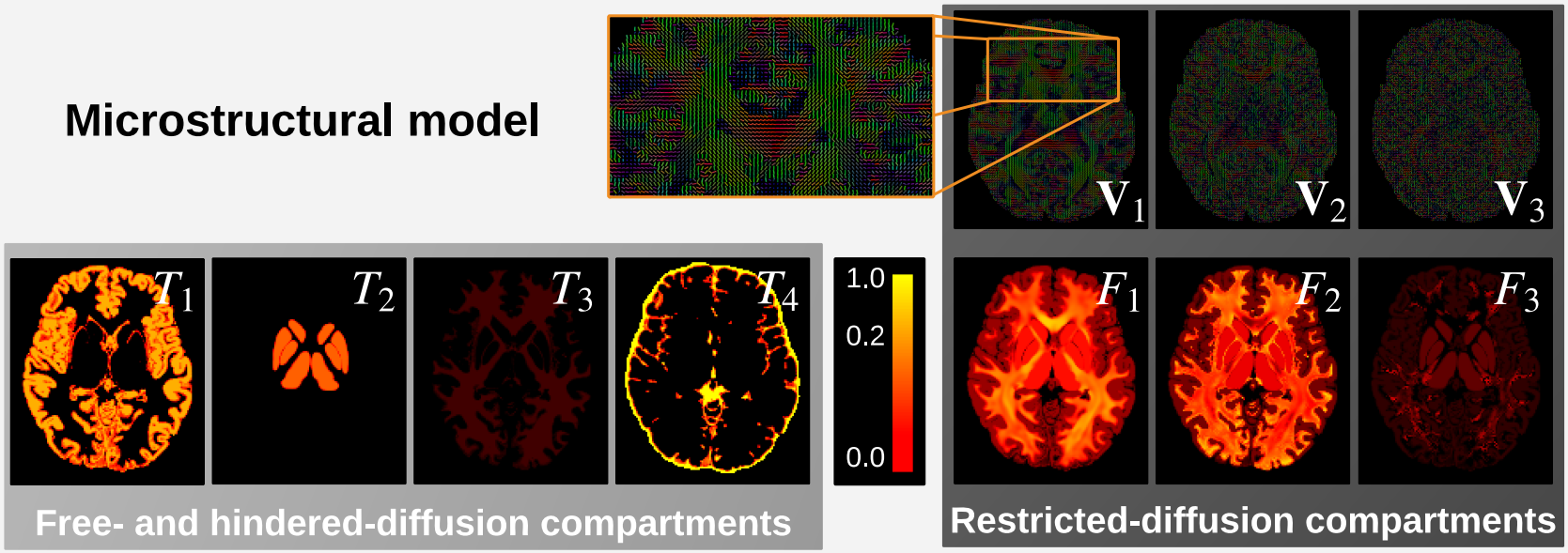


Data: The Human Connectome Project (HCP)

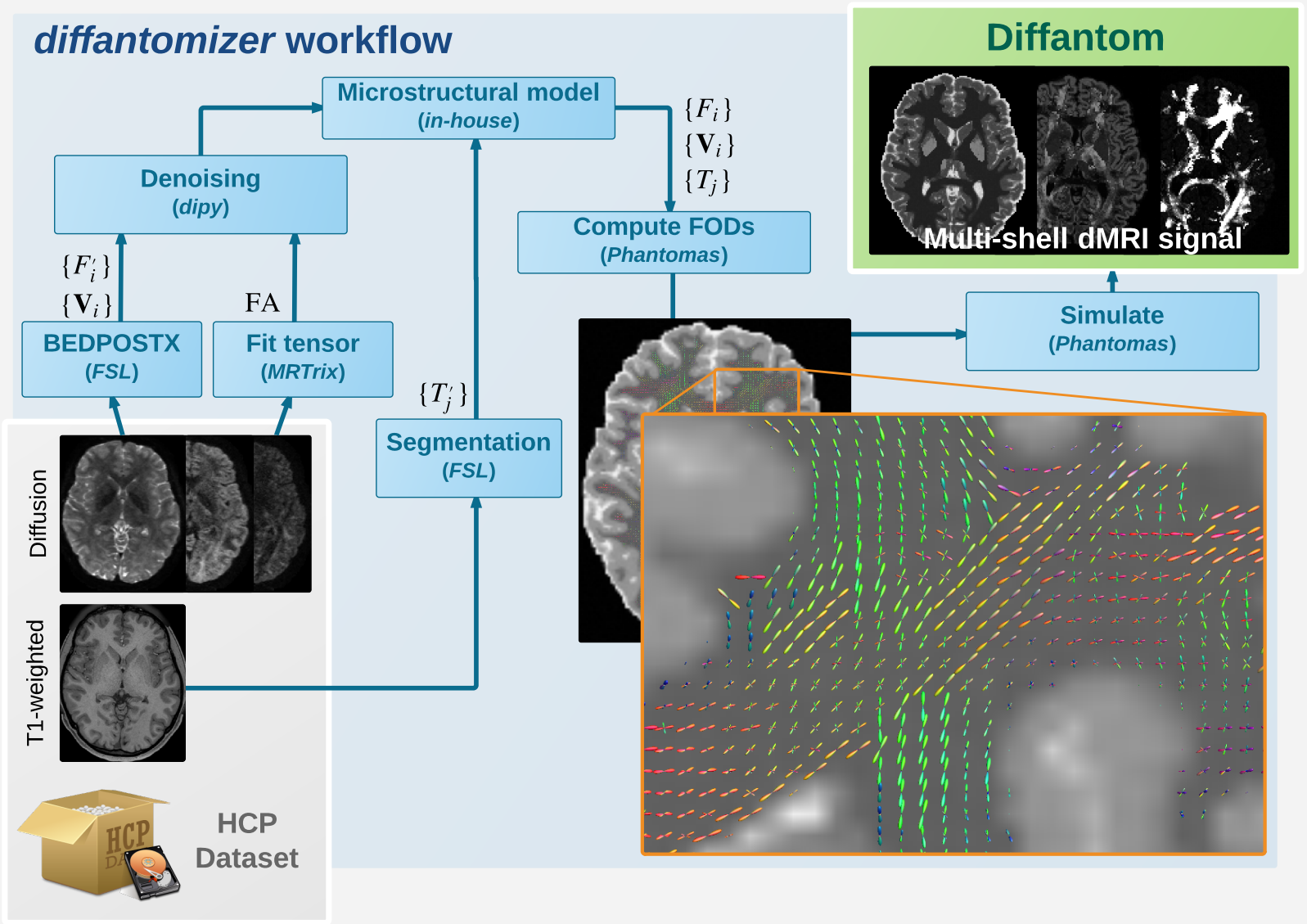
- Two large consortia under a 5yr. project of the NIH.
- Acquiring **high-standard**, research-oriented data (Van Essen and Ugurbil, 2012).
- Data are curated and preprocessed (Glasser et al., 2013). Therefore **distortion *free***.
- We use them extensively to generate gold standards.

Diffantom: introduction & microstructural model

- Whole-brain phantoms are derived from real datasets.
- Inspired by Wilkins et al., 2015:
  - CHARMED (Assaf and Basser, 2005) model.
  - Real datasets are corrected for distortions.
- *Phantomas* simulates signal.
- Microstructural model derived from the real dataset:

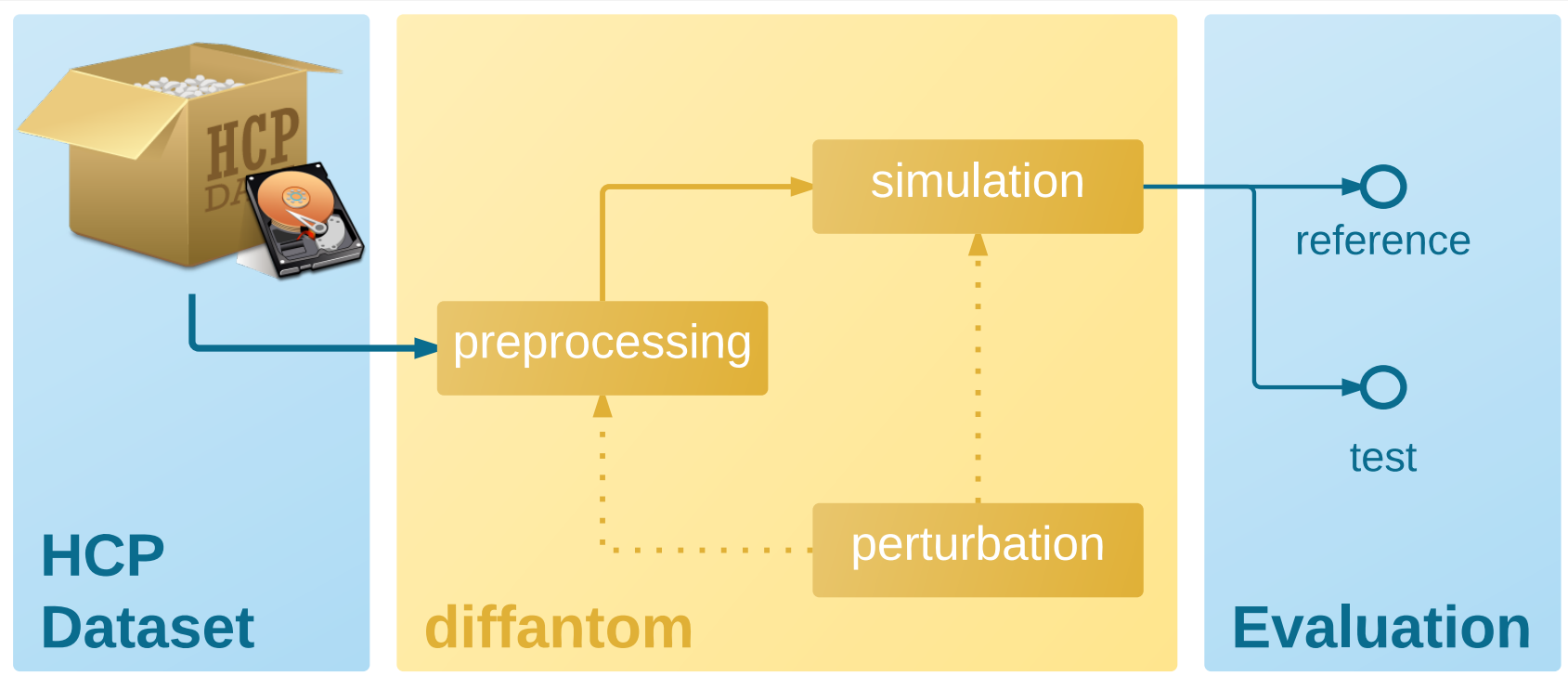


The diffantomizer workflow



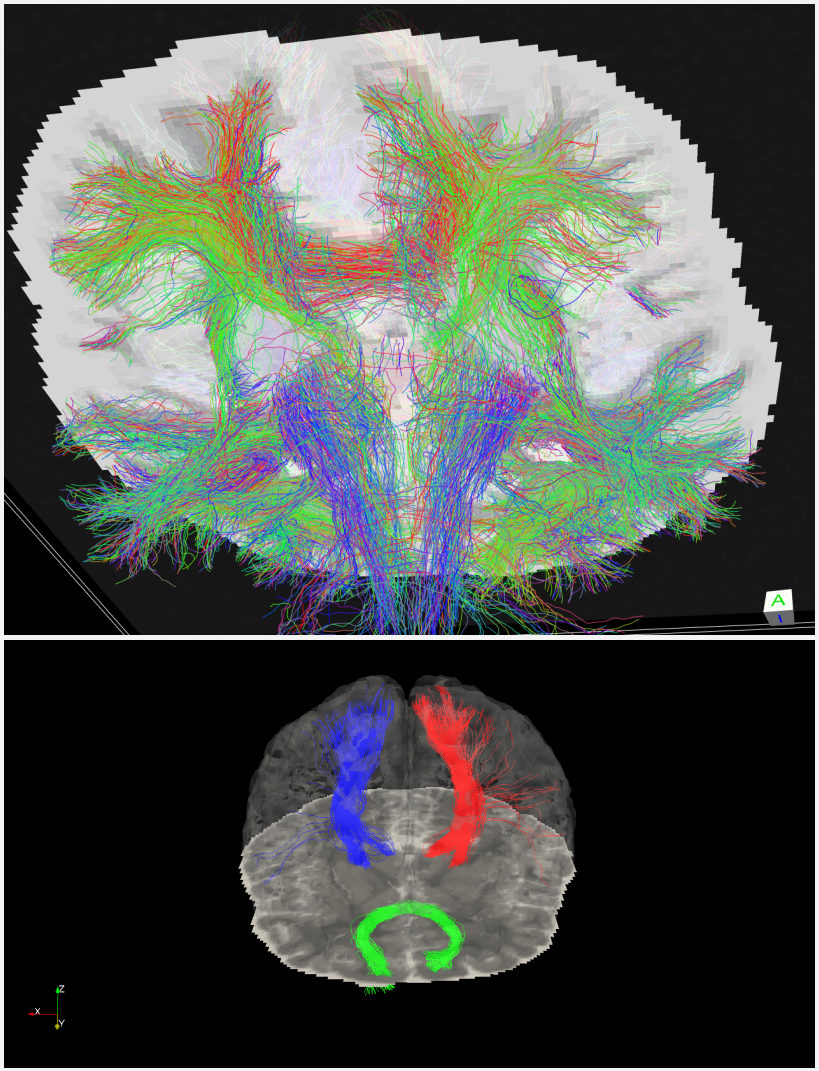
Use of Diffantom

- *Diffantom* is openly available (doi:10.5061/dryad.4p080).
- The *diffantomizer* workflow is open source.
- We created a *Diffantom* with emulated EPI distortion, following this model:

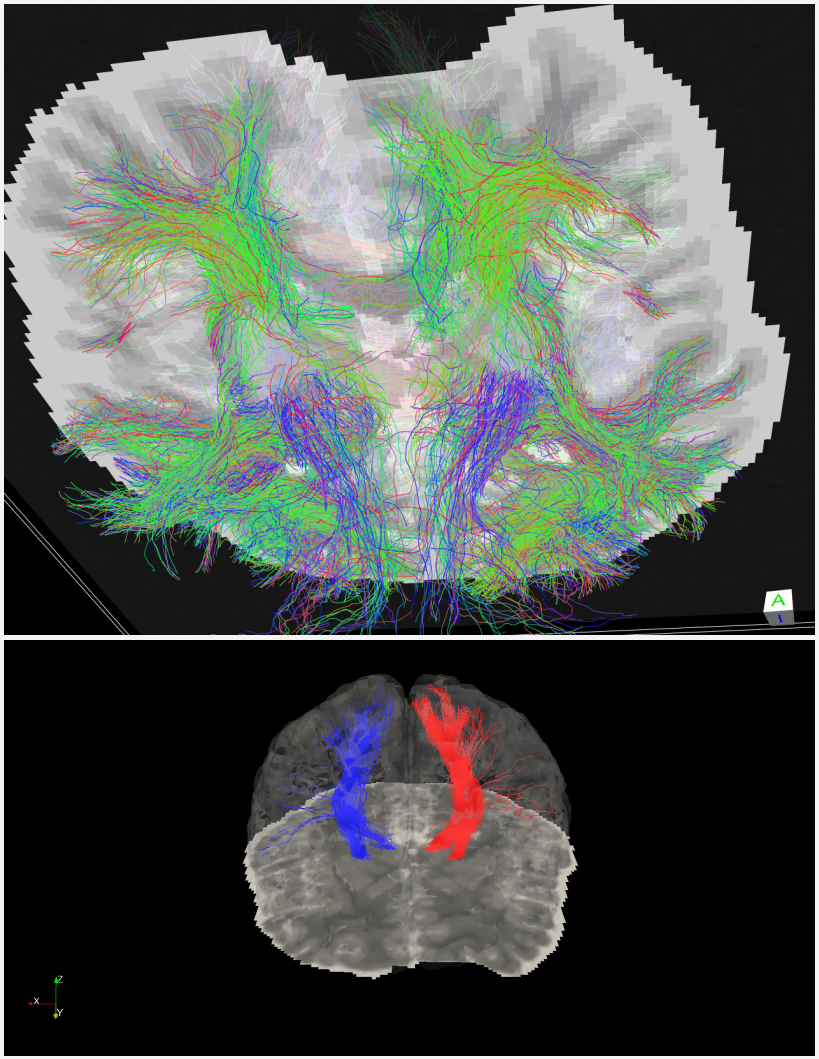


Diffantom: tractography and illustrative bundles

Undistorted



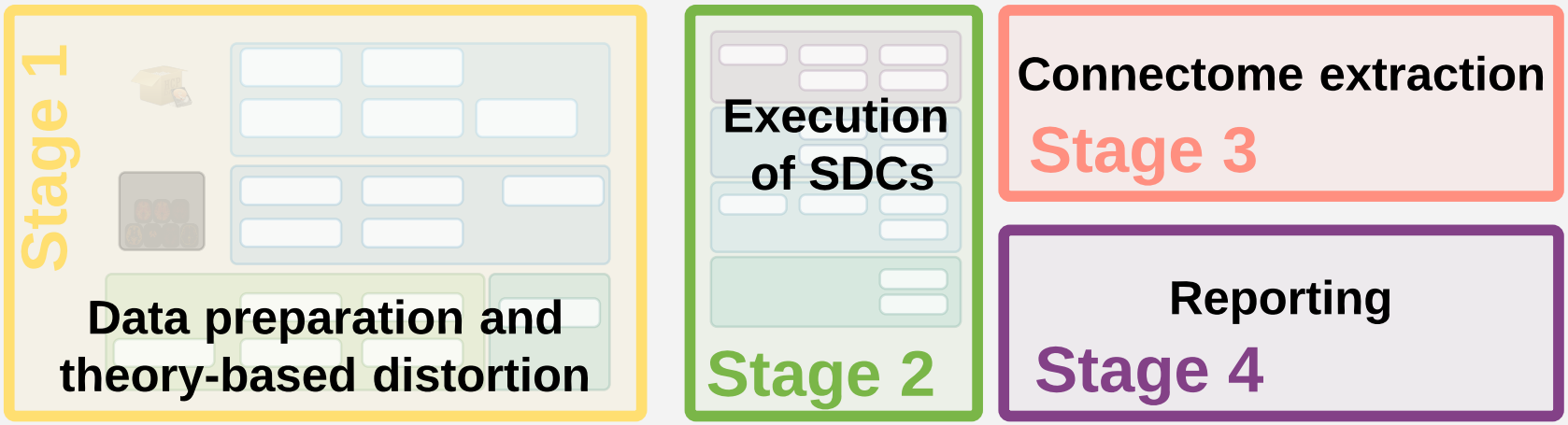
EPI distortion simulated



- Tractography using ACT, tracts segmentation using *track_querier* (Wassermann et al., 2013).

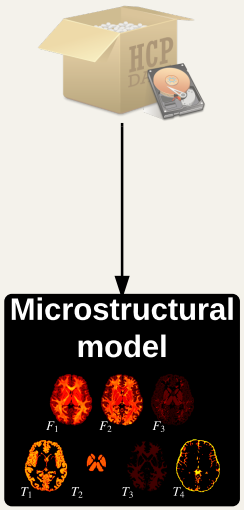
The PySDCev evaluation framework

- Aim: evaluating EPI distortions, and comparing SDCs at the whole-brain scale.
- Measures include investigating the impact on networks.
- Integrates the *diffantomizer*.

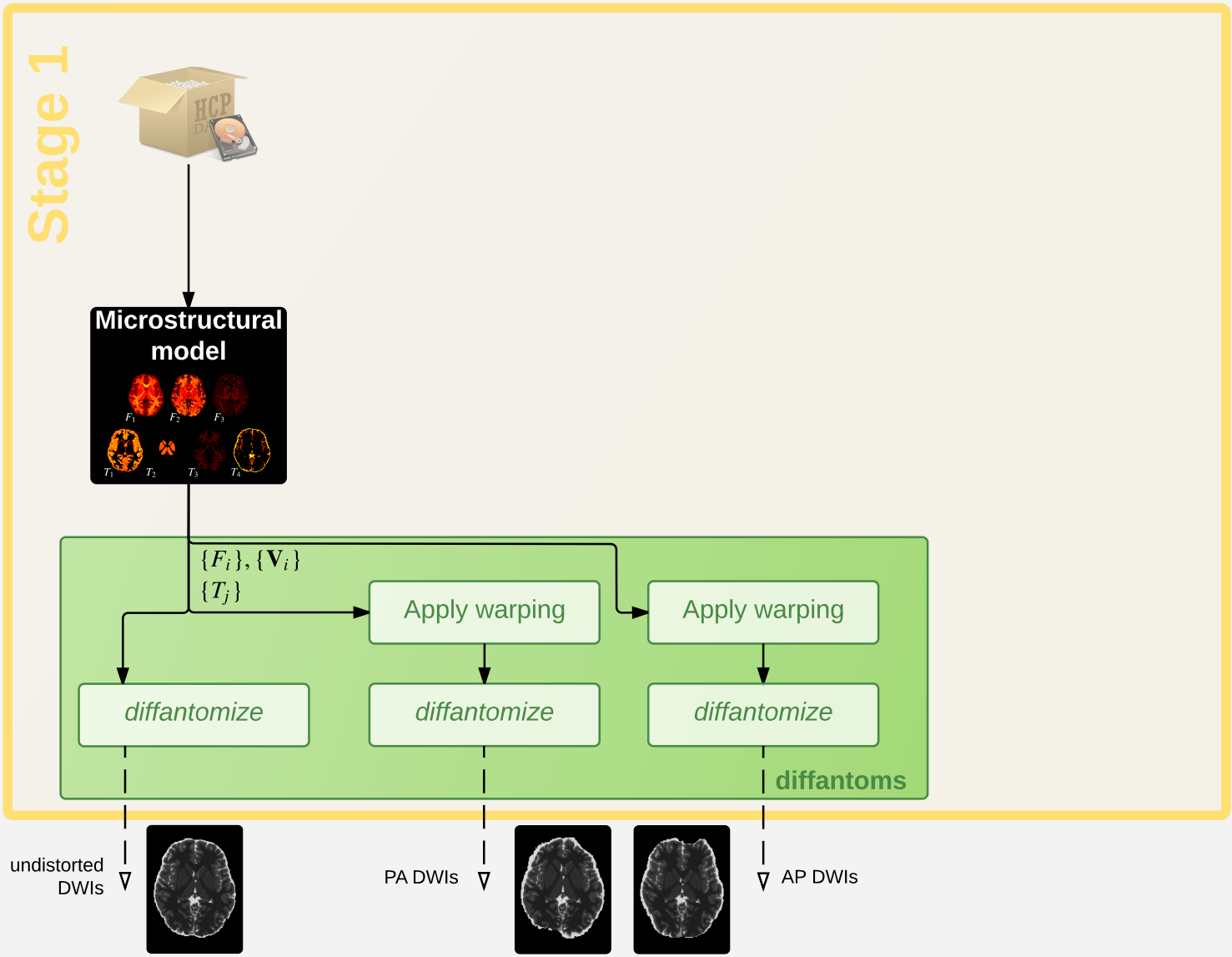


PySDCev, Stage 1

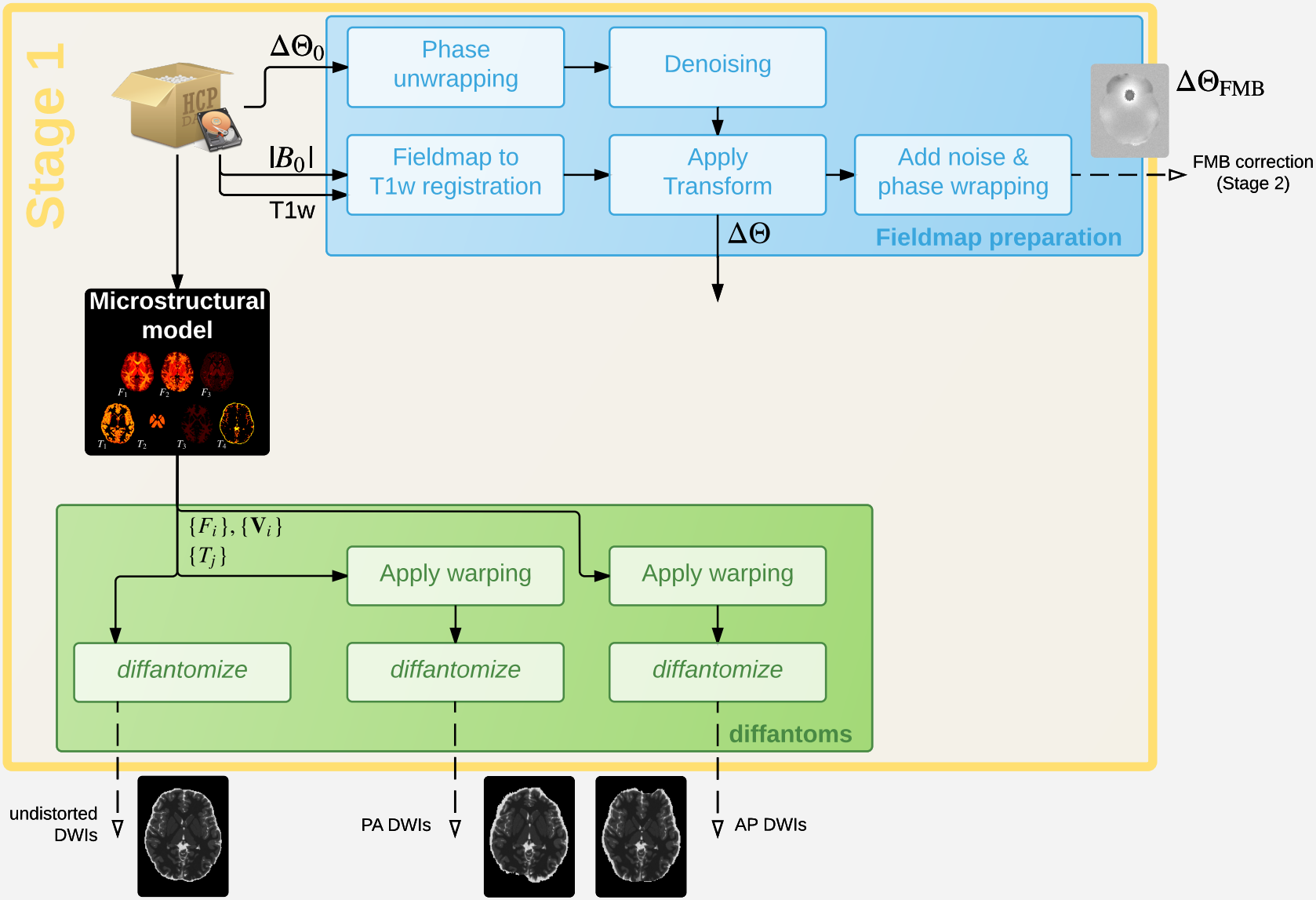
Stage 1



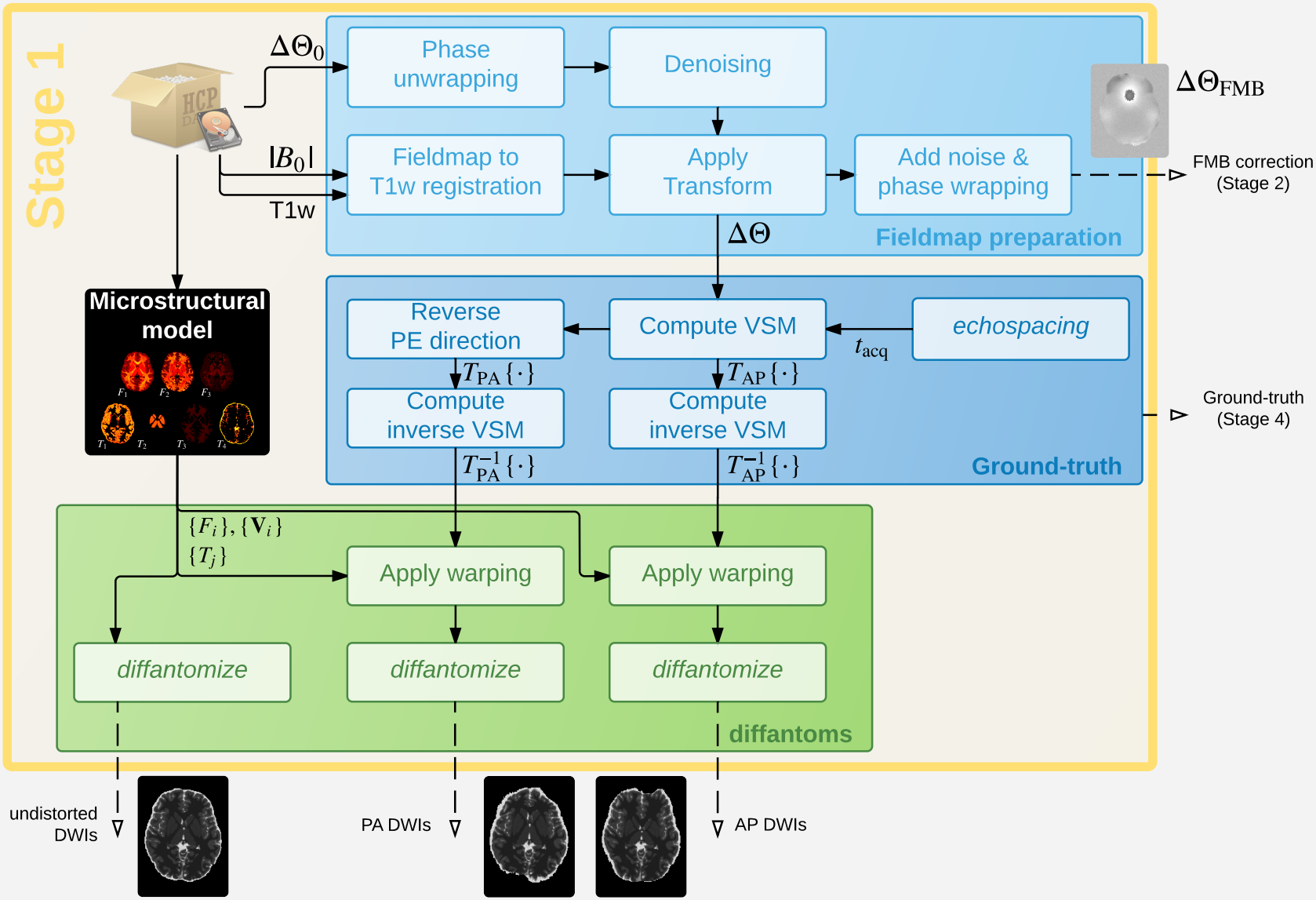
PySDCev, Stage 1



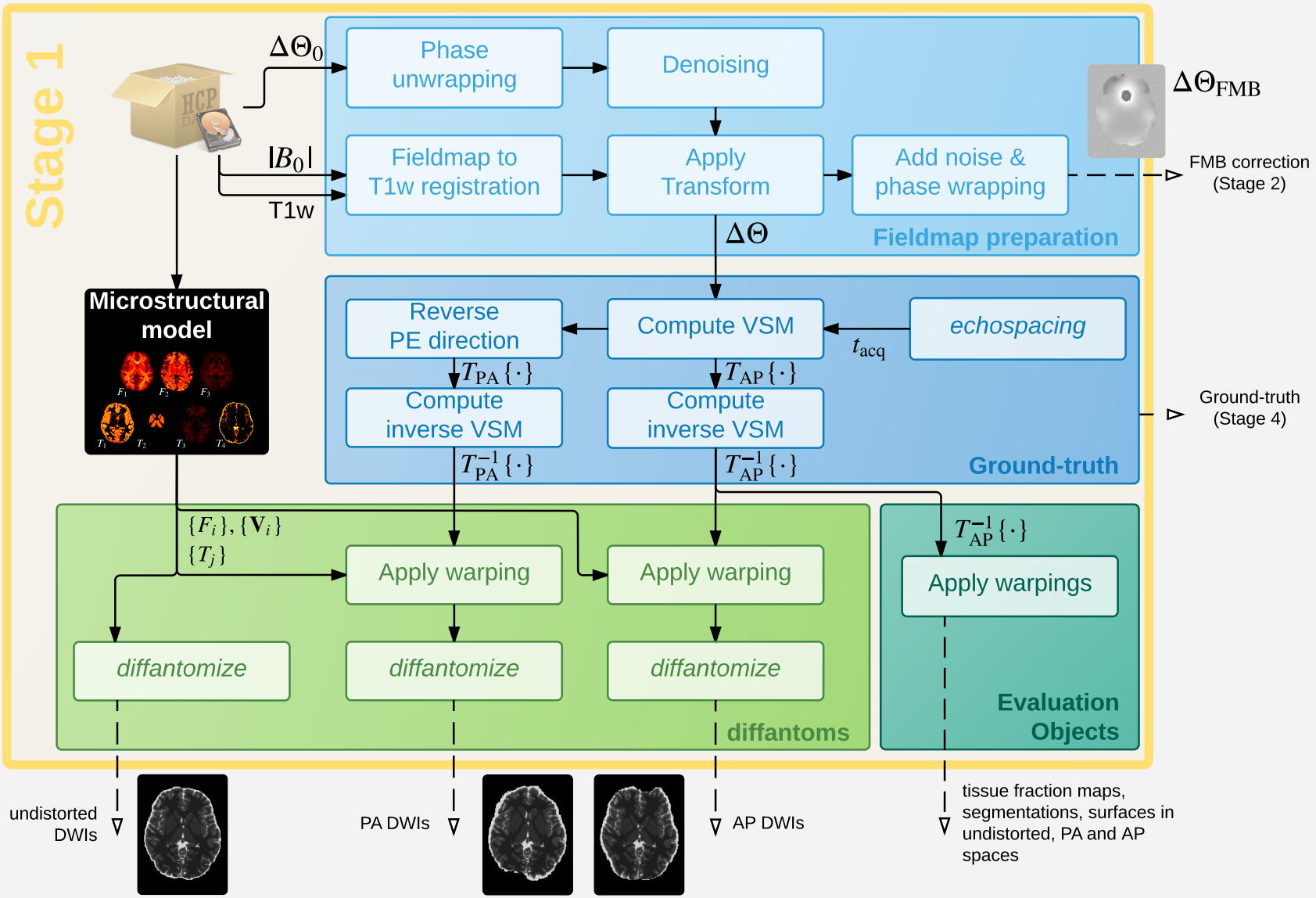
PySDCev, Stage 1



PySDCev, Stage 1

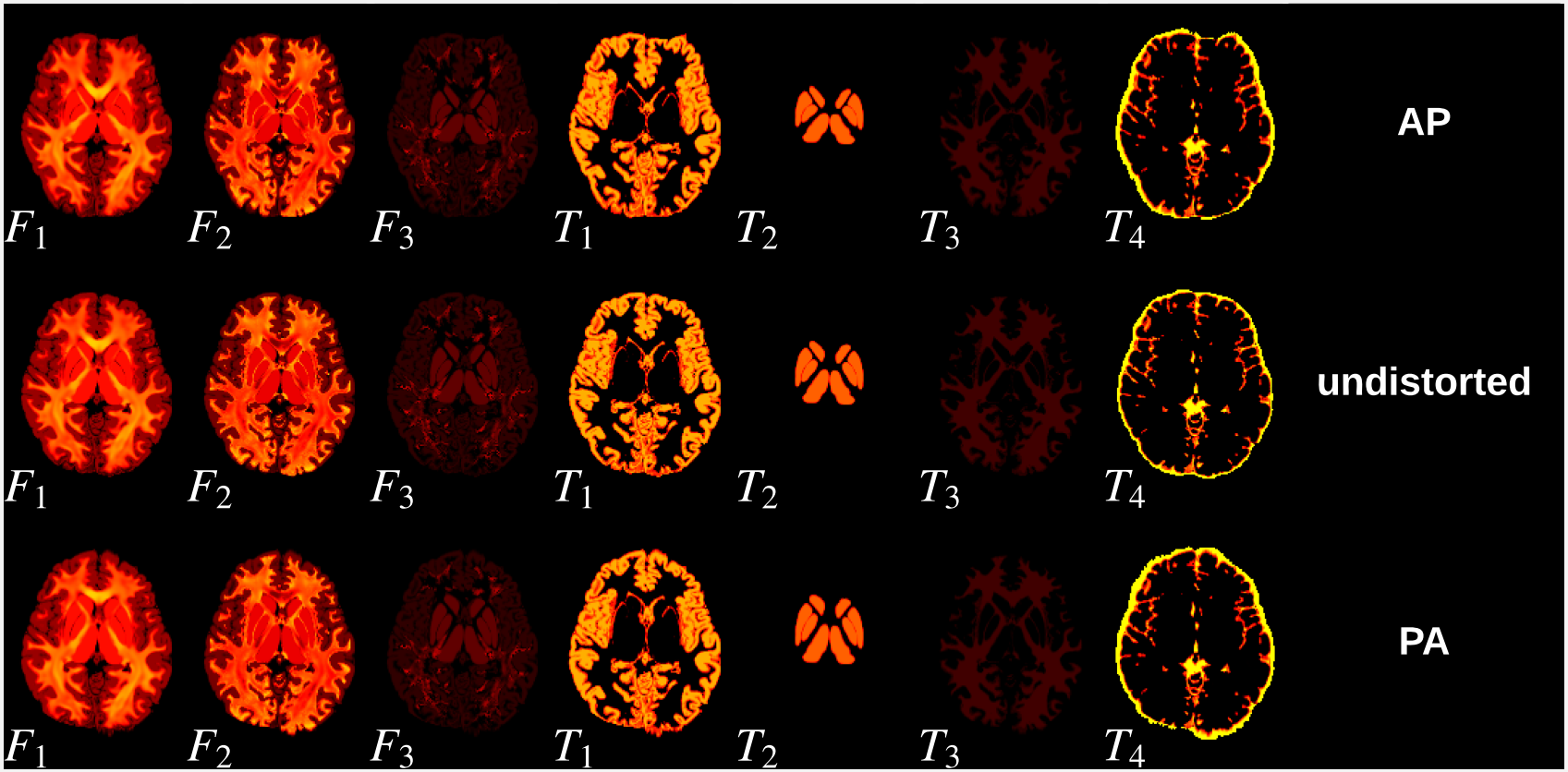


PySDCev, Stage 1



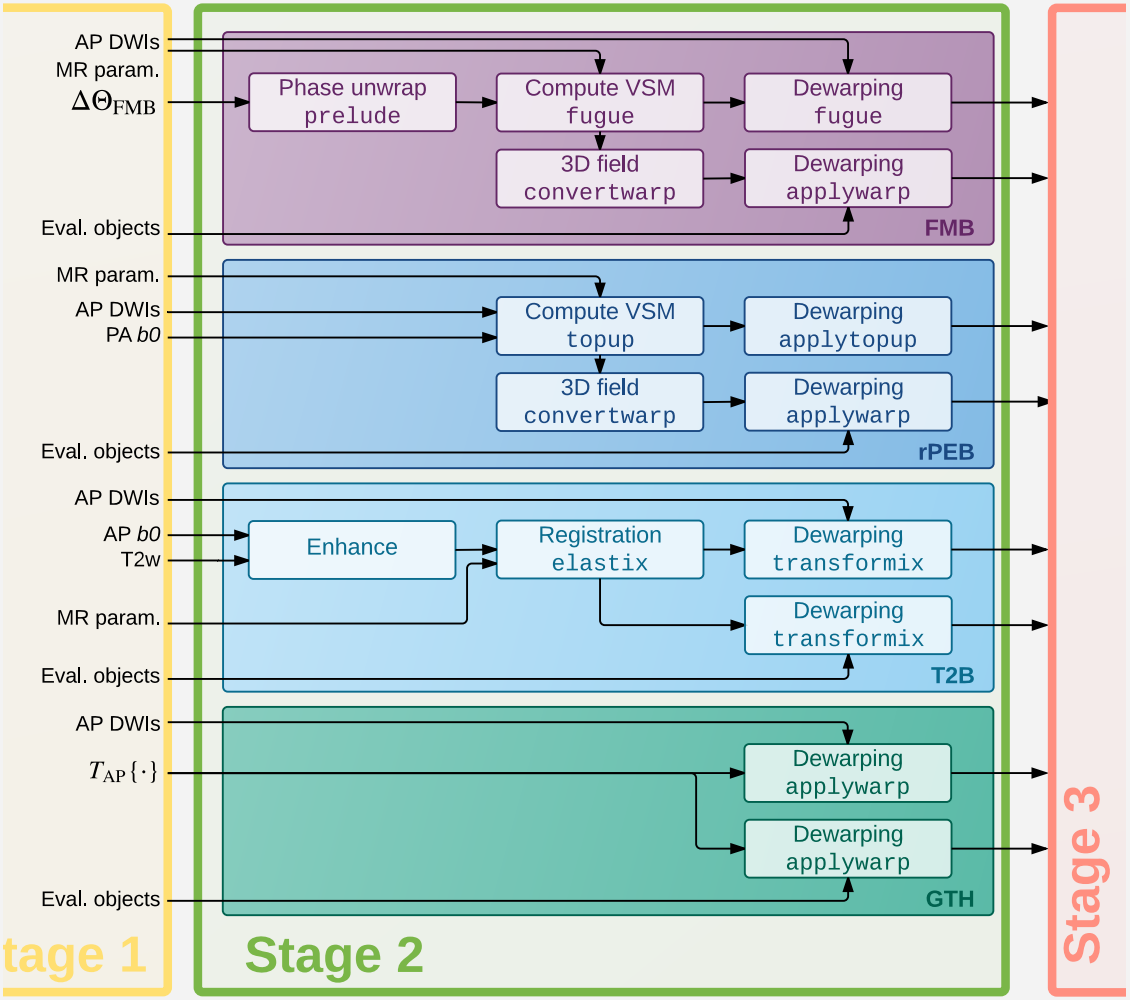
PySDCev, Stage 1

- How the microstructural model of *Diffantom* is distorted:



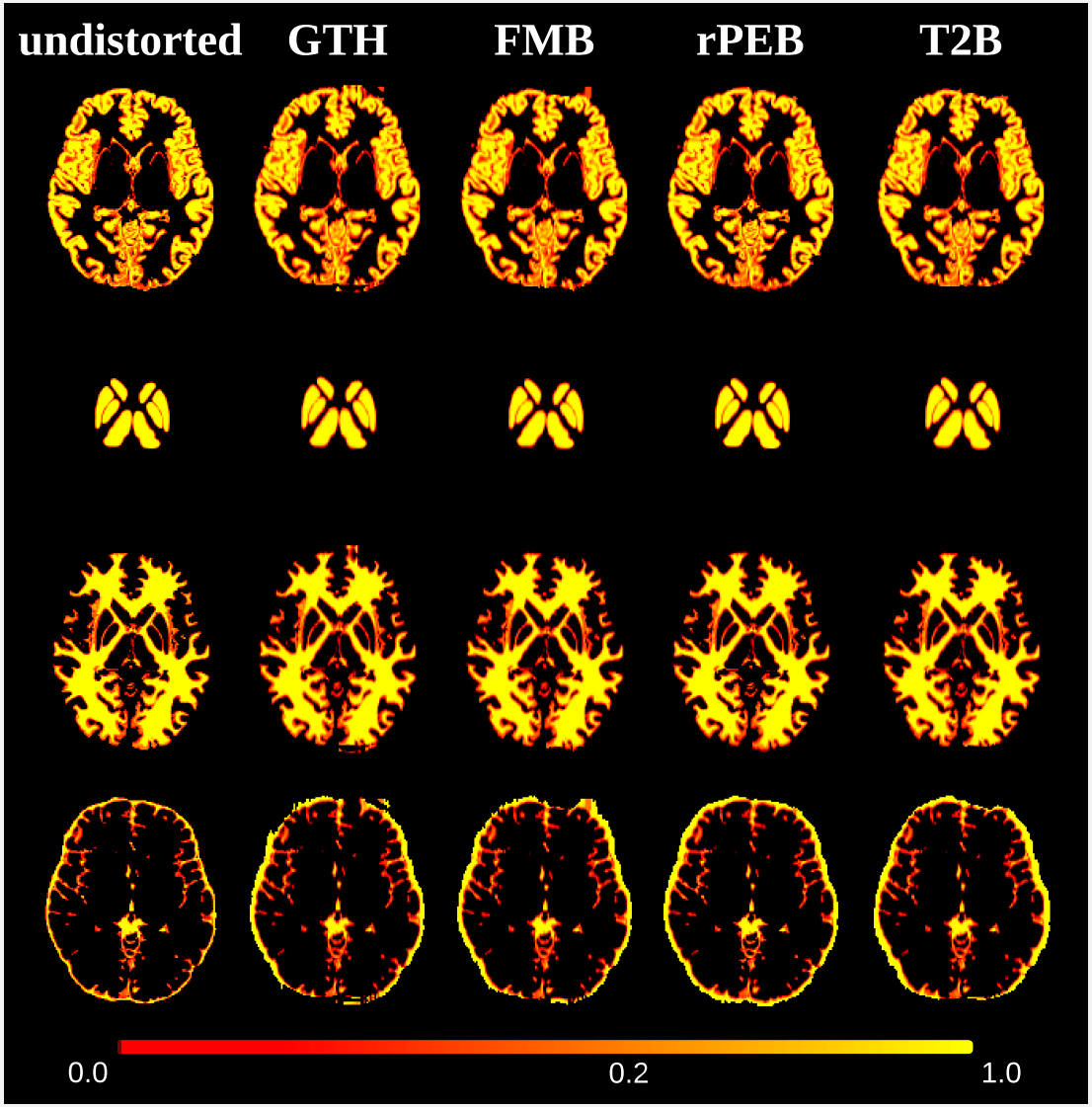
- ... ultimately avoiding DWI signal interpolation.

PySDCev, Stage 2



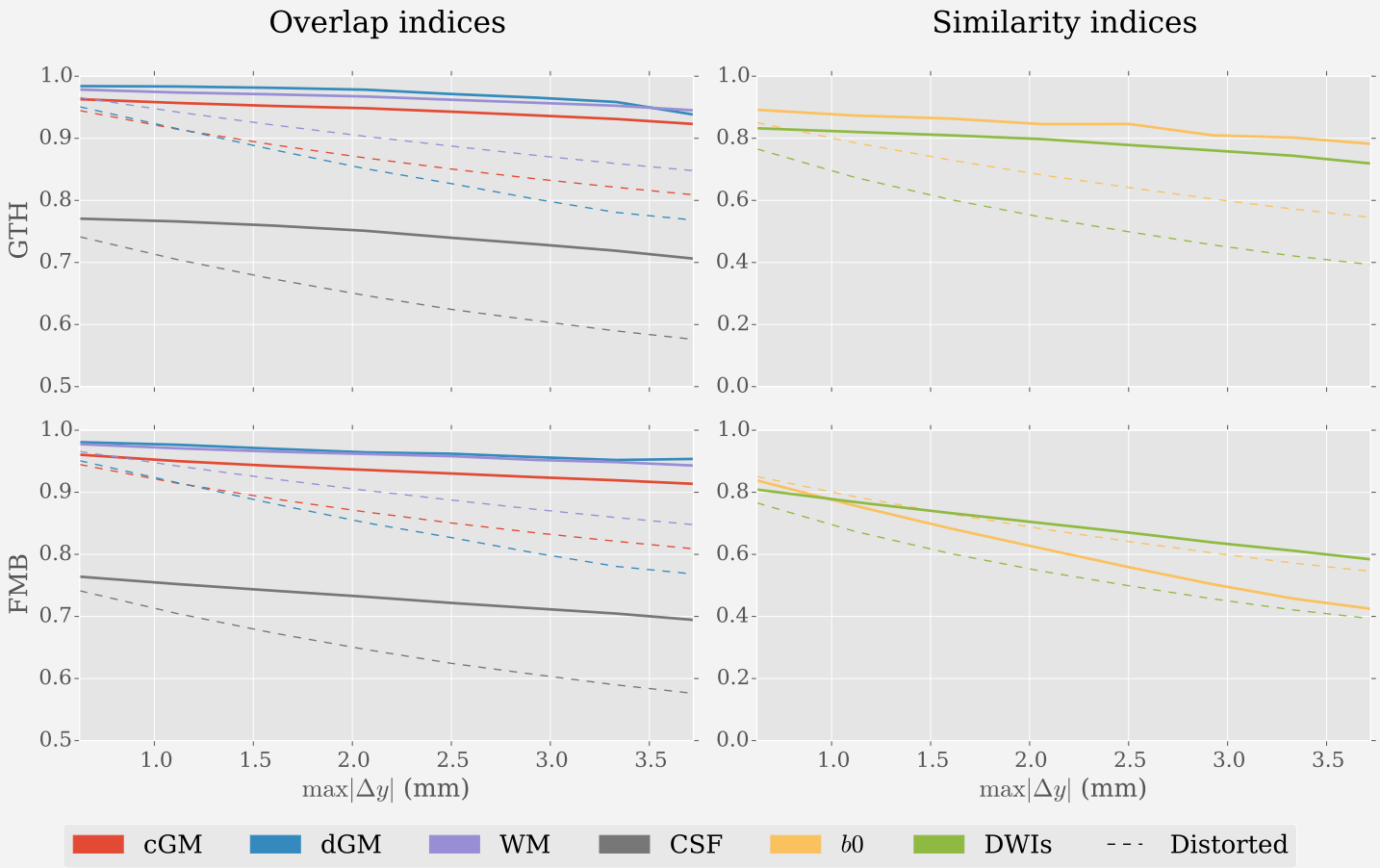
- GTH is a ground-truth reference workflow using the known distortion.

Results - Geometrical accuracy (visually)



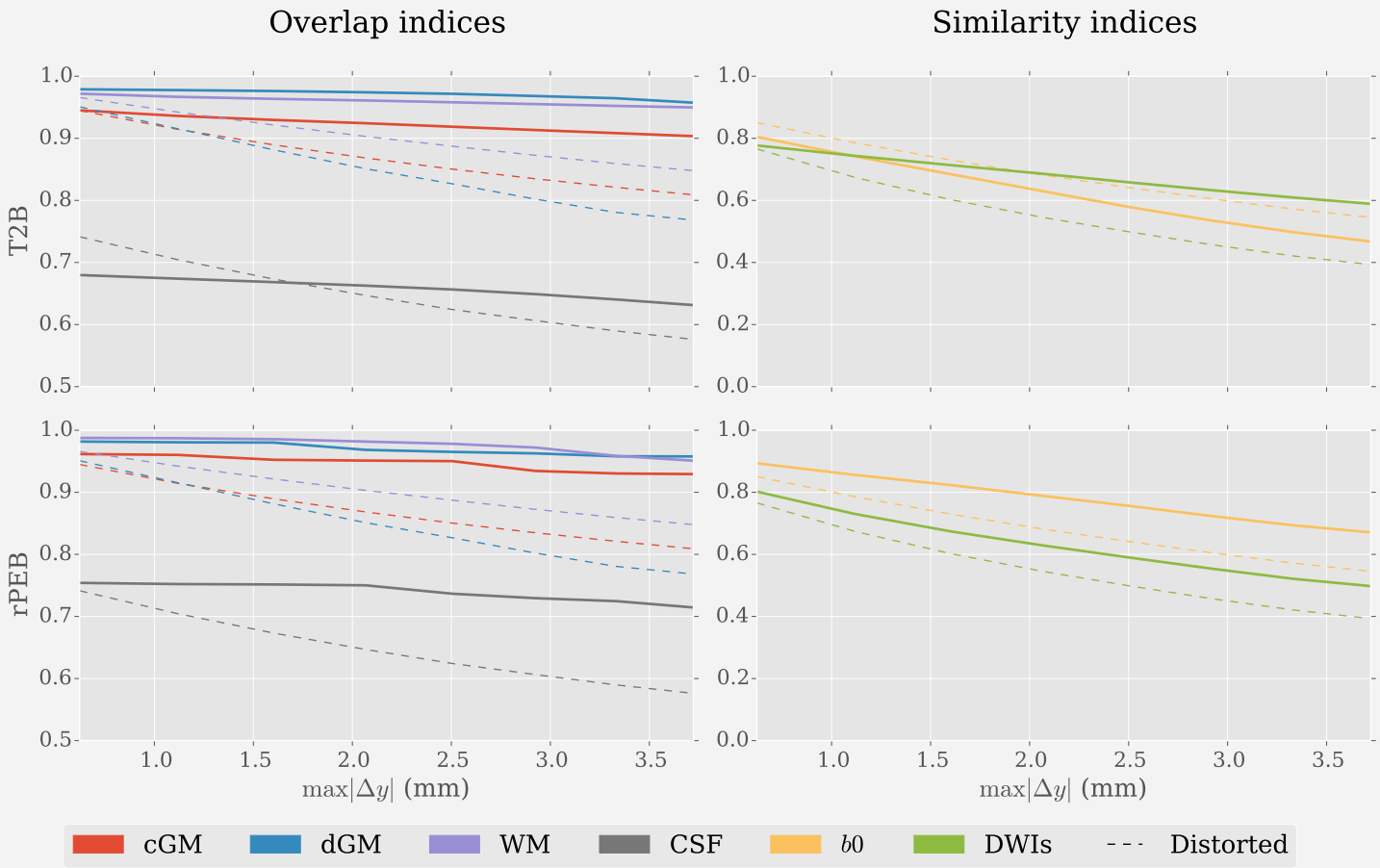
Results - Geometrical accuracy (quantitative)

- Quantitative evaluation of overlap of tissues, and similarity between original and recovered signal.

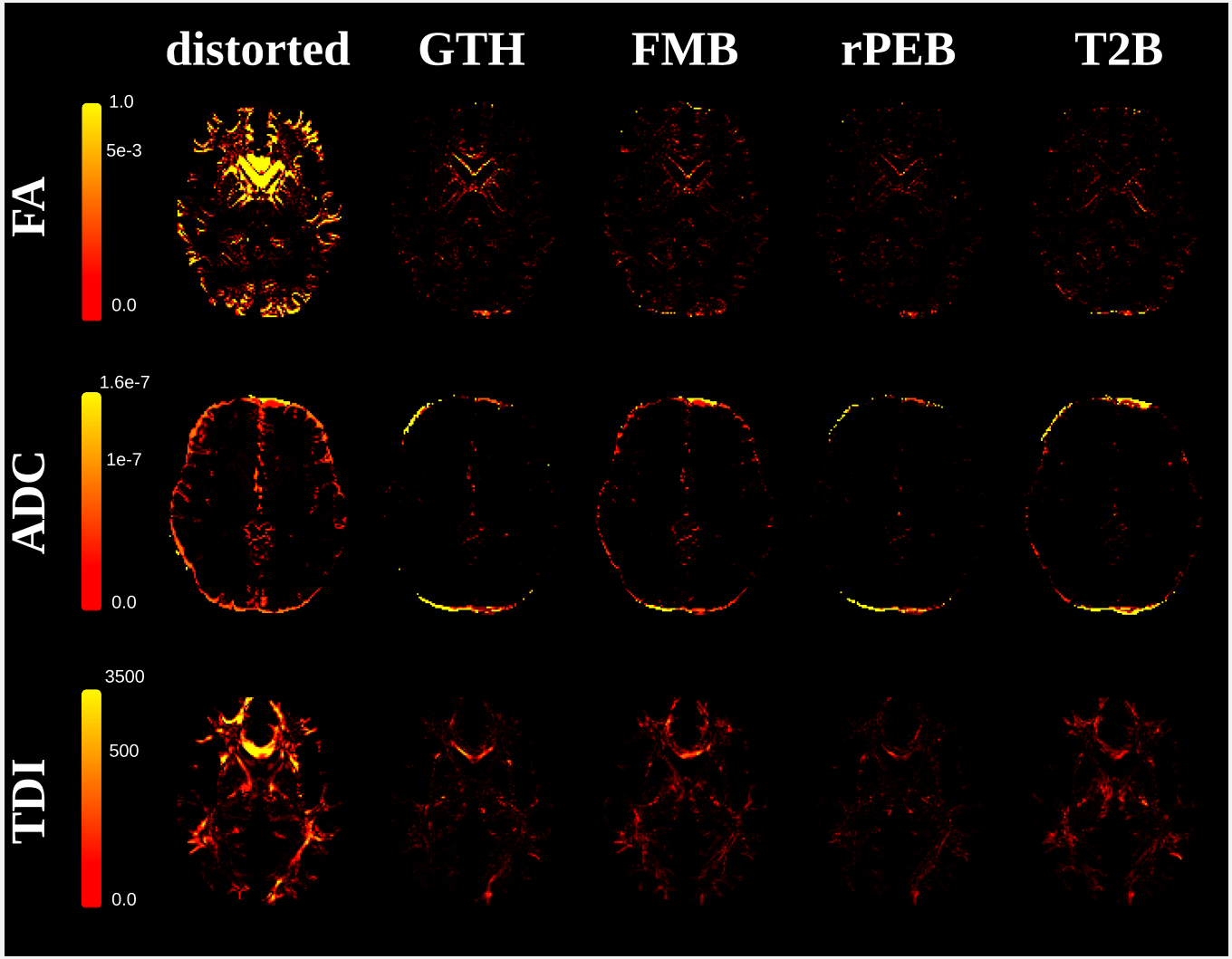


Results - Geometrical accuracy (quantitative)

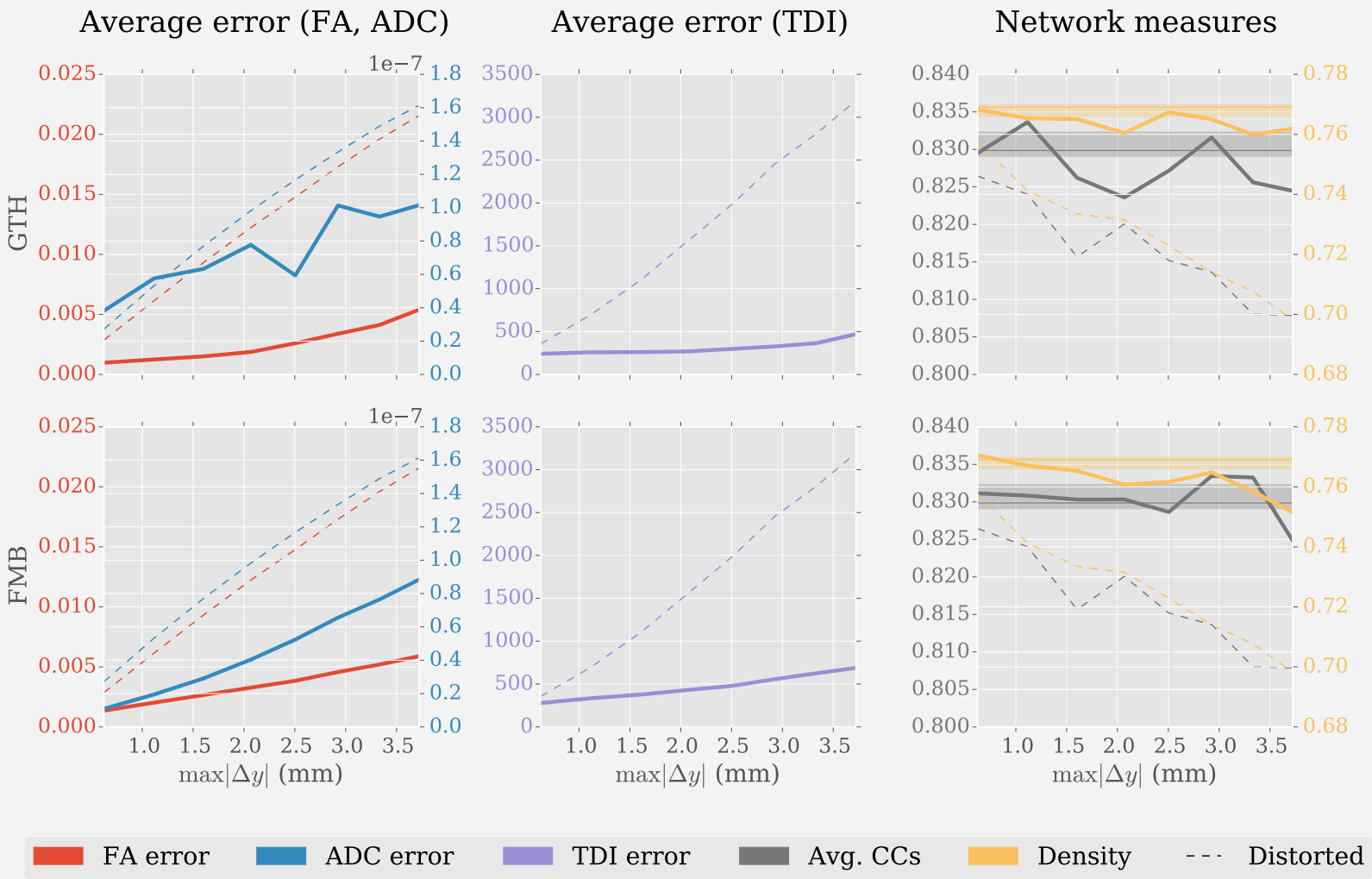
- Quantitative evaluation of overlap of tissues, and similarity between original and recovered signal.



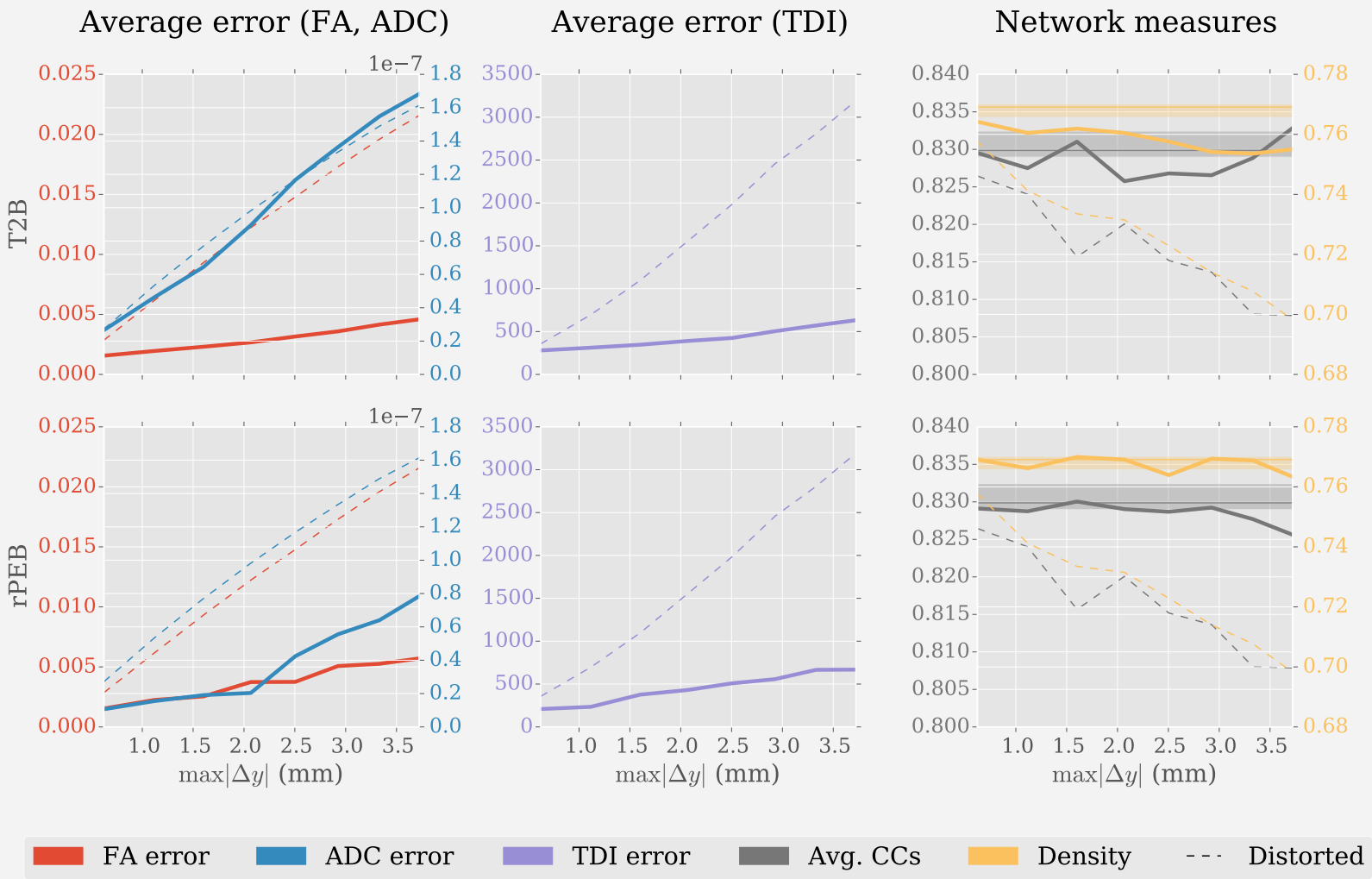
Results - Error maps (visually)



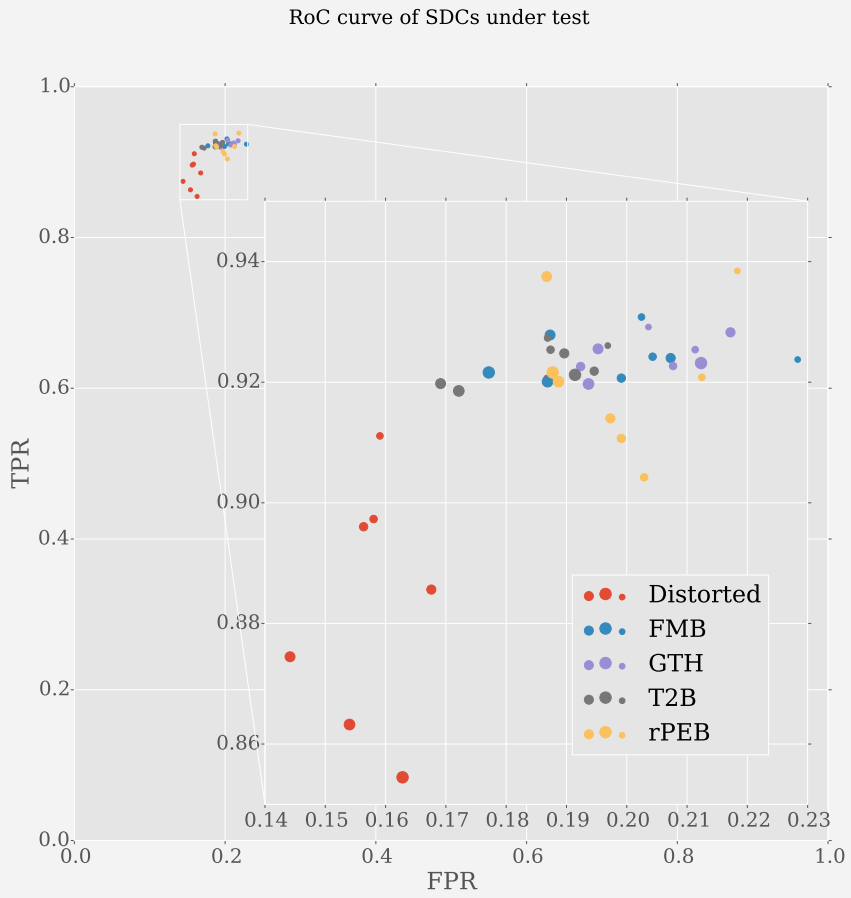
Results - Quantitative evaluation of impact (I)



Results - Quantitative evaluation of impact (II)

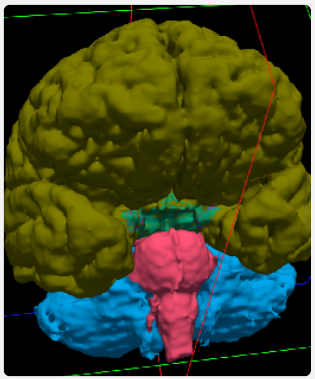


Results - RoC analysis



- Corrections ***are not cost-less***: improvement on sensitivity implies a loss on specificity.
- The GTH distortion (using the known mapping) does not perform better than SDCs. Thus, **any interpolation of DWIs** introduces many FPs.

Regseg, a simultaneous registration and segmentation method



Structural surfaces

regseg

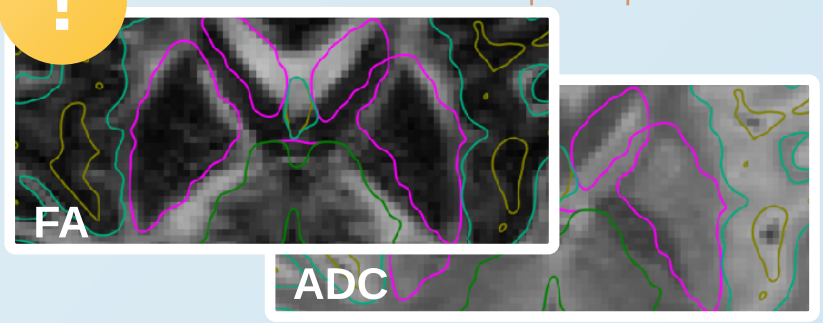
- Surface-to-image registration
- Registration driven by shape-gradients on a Bayesian segmentation framework
- Target image is multivariate: FA&ADC for dMRI datasets

Affine mapping

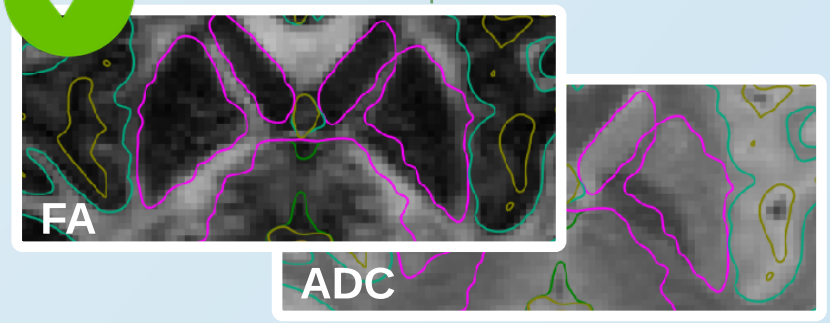
PE aligned, nonlinear mapping

dMRI space (distorted)

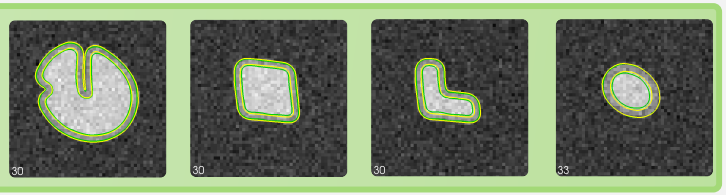
Misregistration error because of EPI distortion:
an additional correction step is required



Structural information correctly mapped into dMRI:
correction is not required



- Proof-of-concept on synthetic phantoms without directional restrictions on the deformation
- Sub-pixel accuracy on both phantoms and 16 real datasets from the Human Connectome Project



Registration and segmentation model

- Registration to map a set of surfaces $\mathbf{\Gamma}$ into M:

$$U\colon \mathbf{\Gamma} \subset \mathbb{R}^n \to M \subset \mathbb{R}^n$$
$$\mathbf{r} \mapsto \mathbf{r}' = \mathbf{r} + \mathbf{u}(\mathbf{r}).$$

- Bayes' rule on the regions $\mathbf{\Omega}$ defined by the projected $\mathbf{\Gamma}$:

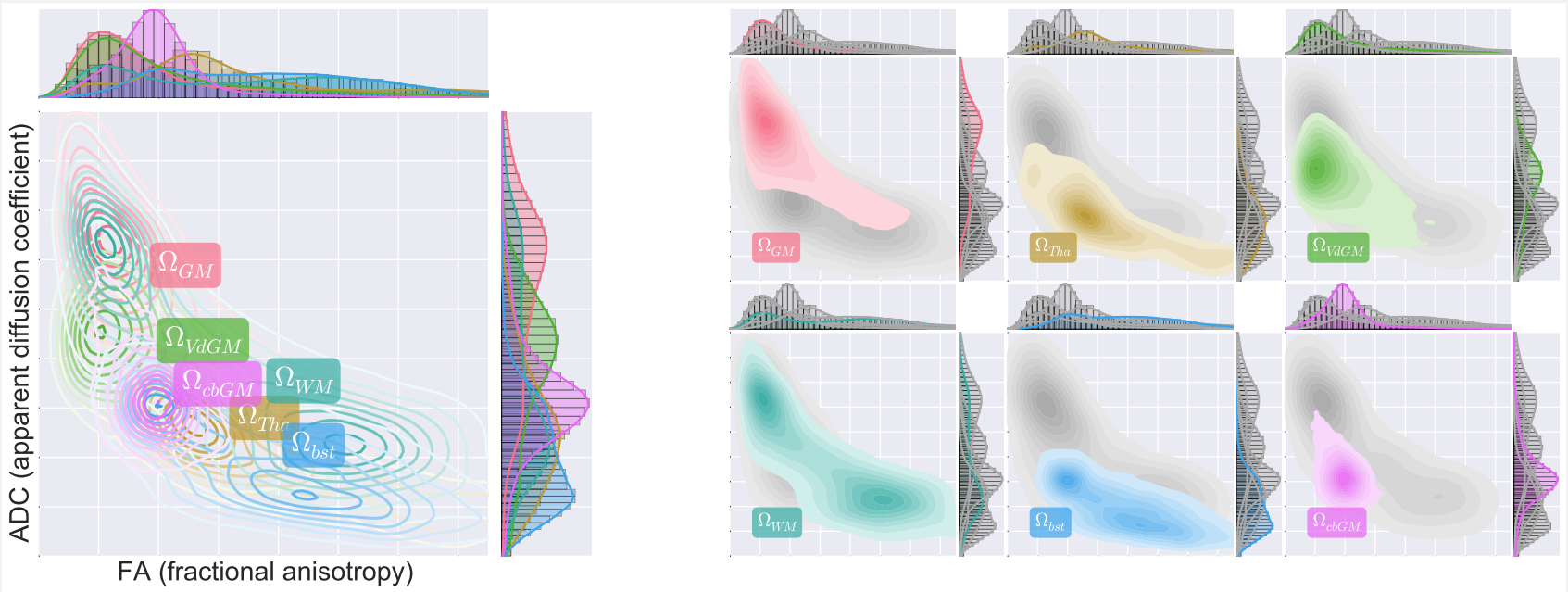
$$P(U \mid M, \mathbf{\Omega}) = \frac{P(M \mid U, \mathbf{\Omega})\, P(U)}{P(M)}.$$

- Homogeneus regions Ω_l modeled with multivariate normal distributions:

$$P(M \mid U) = \prod_l \prod_{\mathbf{r}\in\Omega_l} \frac{1}{\sqrt{(2\pi)^C\ |\mathbf{\Sigma}_l|}}\, e^{\left(-\frac{1}{2}\mathcal{D}_l^2(\mathbf{f}')\right)}.$$

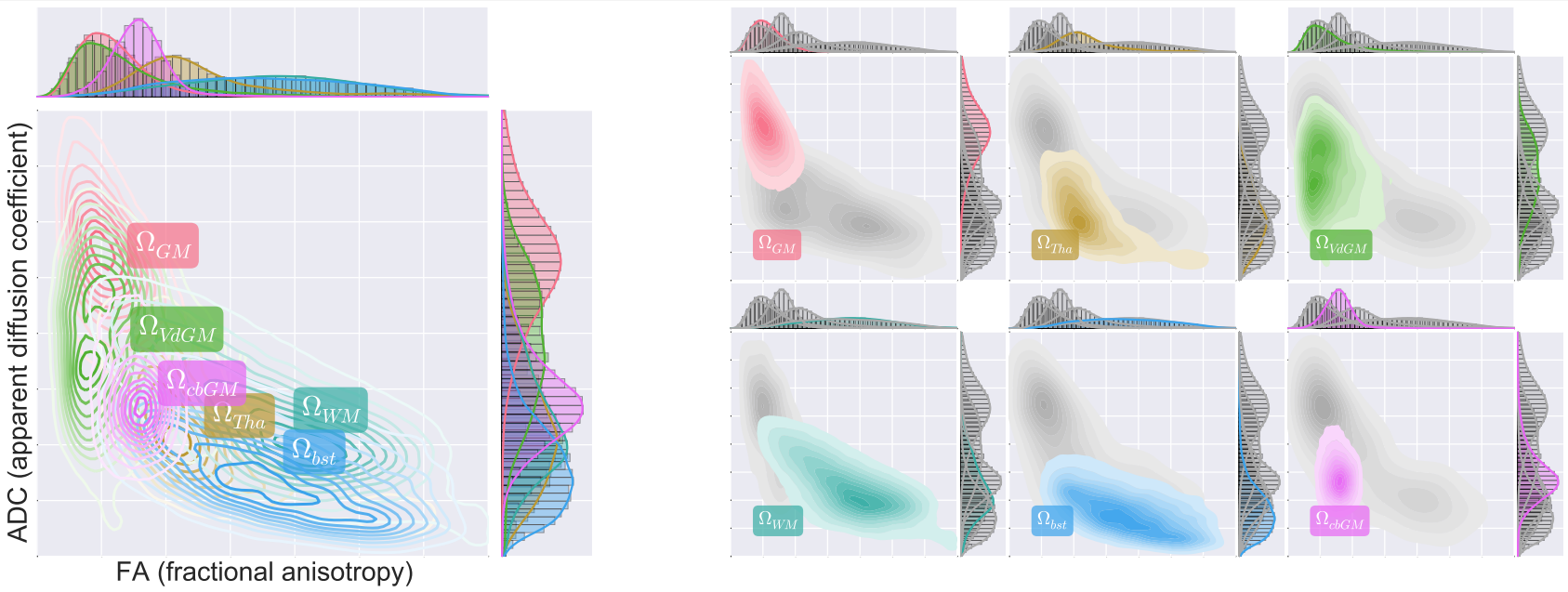
Visual inspection of the segmentation model

- Segmentation of six homogeneous regions Ω_l.
- Indirect minimization of covariances.
- Model with **undistorted** surfaces, imposed on **distorted** data:



Visual inspection of the segmentation model

- Segmentation of six homogeneous regions Ω_l.
- Indirect minimization of covariances.
- Model with **distorted** surfaces, fitted into **distorted** data:



Cost-function of regseg

- Mumford and Shah functional (1989), with the regularization term of Nagel and Enkelmann, 1986:

$$E(\mathbf{u}) = \text{Const.} + \underbrace{\sum_l \int_{\Omega_l} \mathcal{D}_l^2(\mathbf{f}')\, d\mathbf{r}}_{\text{Data term } (E_{\text{data}})} + \underbrace{\int_\Omega \frac{1}{2}\left[\boldsymbol{\alpha}\cdot\mathbf{u}^{\circ 2} + \boldsymbol{\beta}\cdot(\nabla\mathbf{u})^{\circ 2}\right] d\mathbf{r}}_{\text{Regularization term } (E_{\text{reg}})}.$$

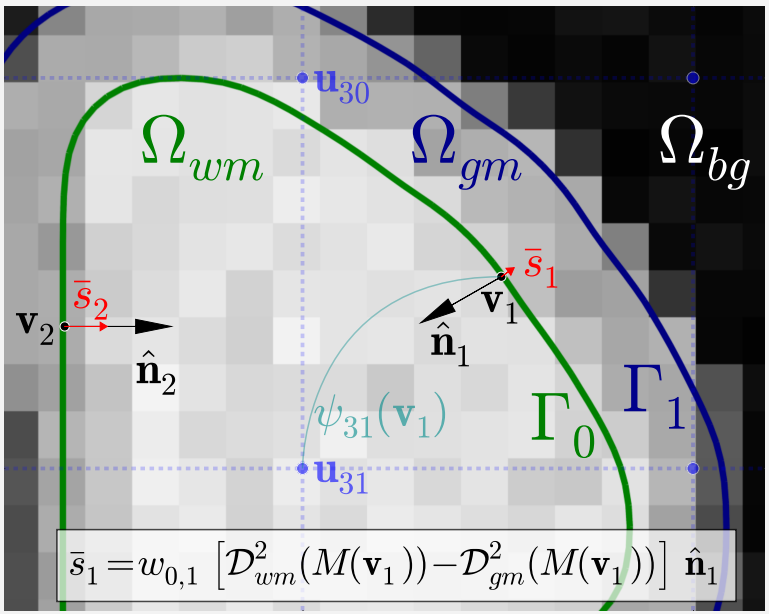
- Gradient-descent minimization:

$$\frac{\partial \mathbf{u}(\mathbf{r},t)}{\partial t} \propto -\frac{\partial E(\mathbf{u})}{\partial \mathbf{u}_k},$$
$$\frac{\partial E(\mathbf{u})}{\partial \mathbf{u}_k} = \frac{\partial E_{\text{data}}}{\partial \mathbf{u}_k} + \frac{\partial E_{\text{reg}}}{\partial \mathbf{u}_k} = \mathbf{g}_k + \frac{\partial E_{\text{reg}}}{\partial \mathbf{u}_k}$$

Shape-gradients

- Compute the derivative of the data term:

$$\mathbf{g}_k = \frac{\partial}{\partial \mathbf{u}_k}\left\{\sum_l \int_{\Omega_l} \mathcal{D}_l^2(\mathbf{f}')\right\} = \frac{\partial}{\partial \mathbf{u}_k}\left\{\sum_l \sum_{\mathbf{x}\in\Omega_l} \mathcal{D}_l^2(\mathbf{f}')\right\}.$$



- Shape-gradients (Herbulot et al., 2006):

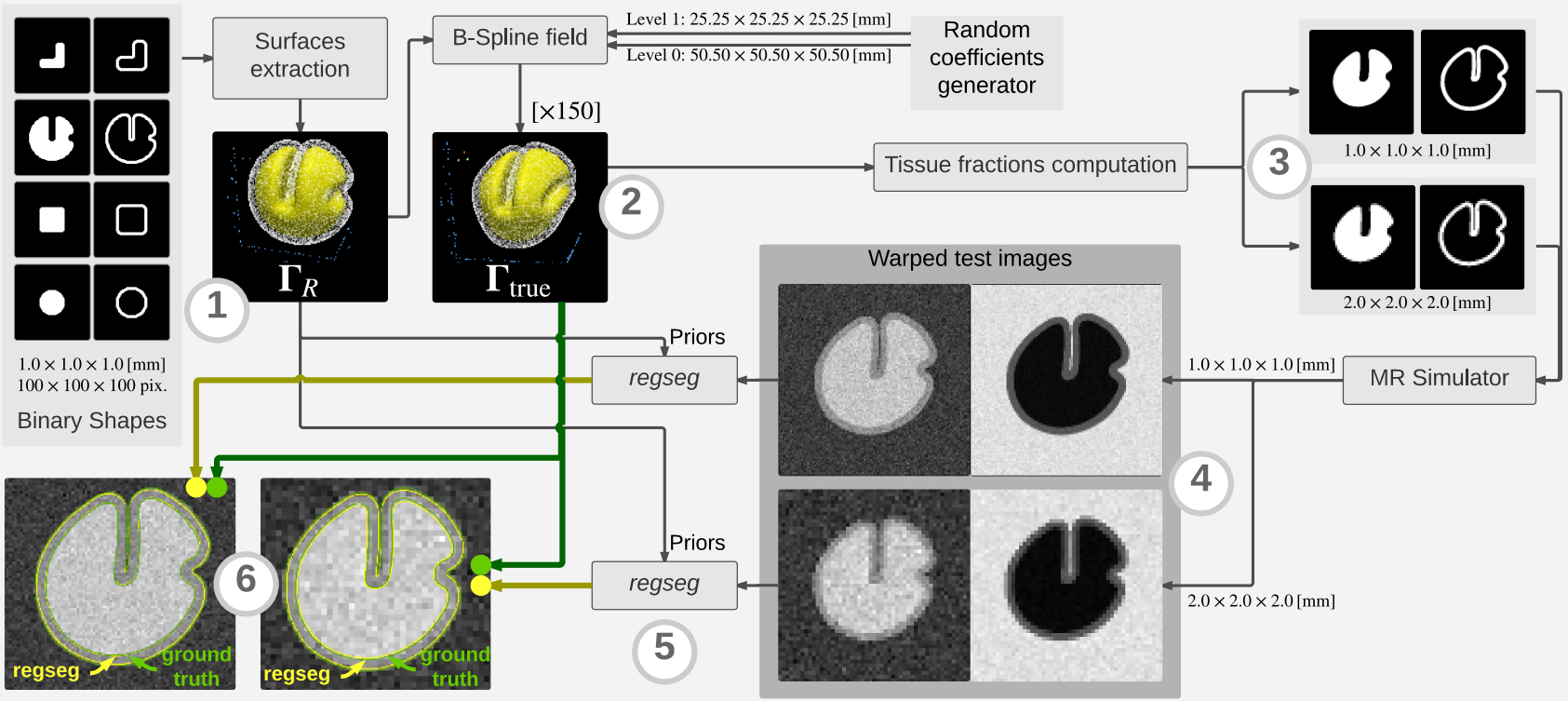
$$\mathbf{g}_k = -\sum_i \bar{s}_i \cdot \psi_k(\mathbf{v}_i)\,\hat{\mathbf{e}} = -\sum_i \mathbf{g}_{i,k}.$$

- Euler-forward system with update equation:

$$\mathbf{u}_k^{t+1} = \mathcal{F}^{-1}\left\{\frac{\mathcal{F}\{\delta^{-1}\mathbf{u}_k^t - \mathbf{g}_k^t\}}{\mathcal{F}\{(\delta^{-1}+\alpha)I - \beta\Delta\}}\right\}.$$

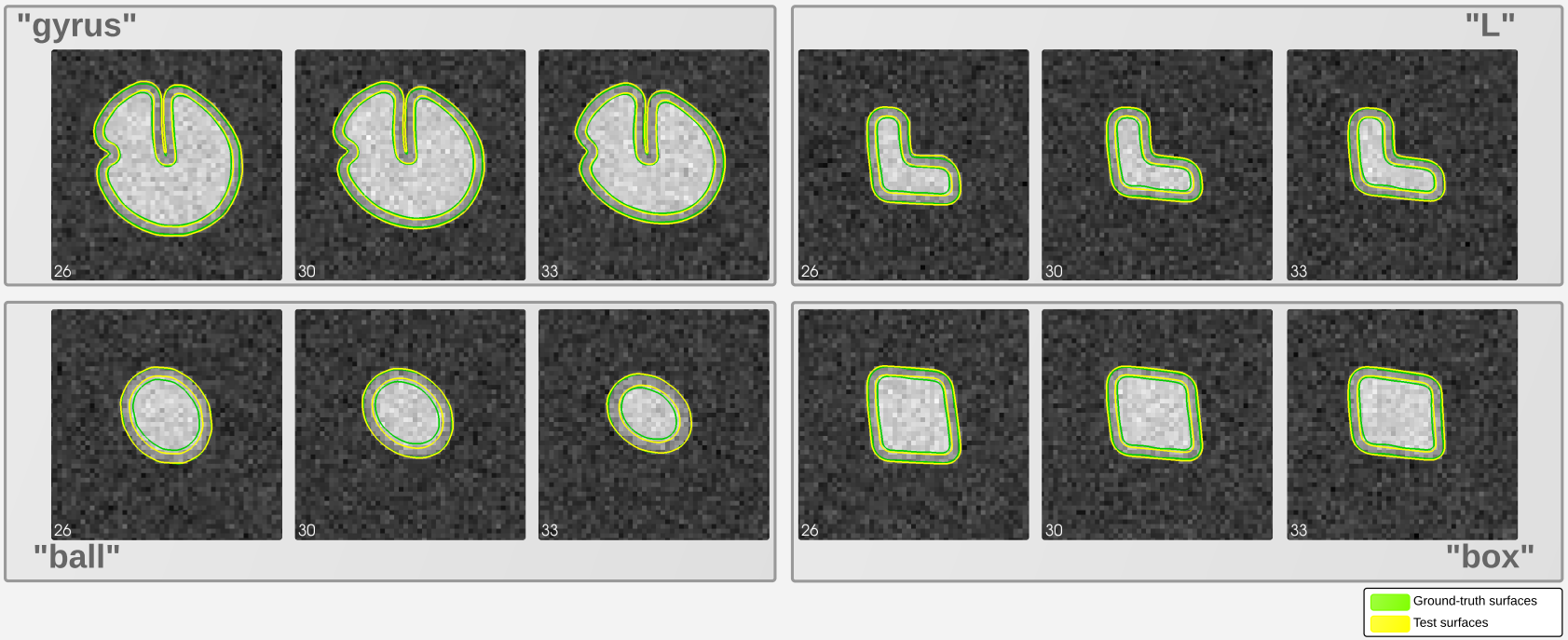
Validating regseg on phantoms (methods)

- **Random distortions**: 1200 experiments (4 model types $\times$ 150 realizations of distortion $\times$ 2 resolutions).
- **Bivariate target-image**: stack of T1w-like and T2w-like.
- **Segmentation model**: 2 surfaces, 3 regions (WM-like, GM-like crust, CSF-like background).



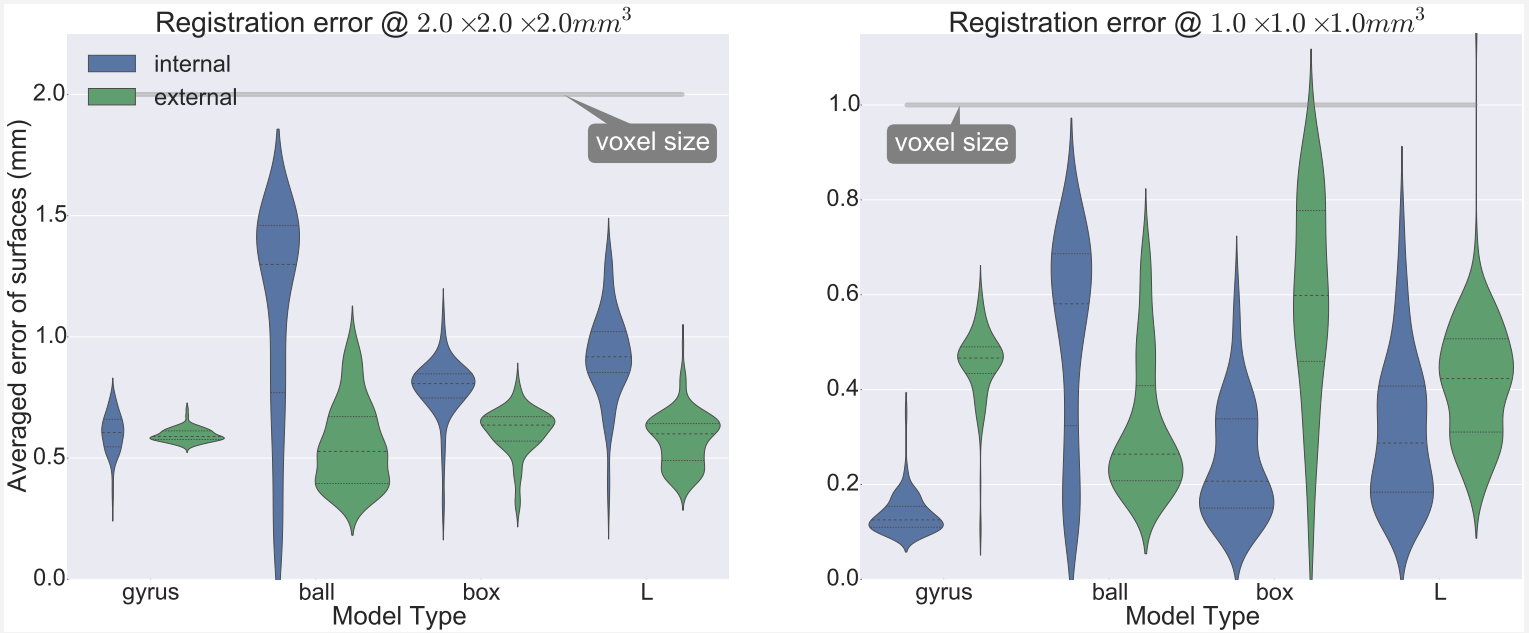
Validating regseg on phantoms (visual)

- **Visual assessment** (coronal views, $x = (26, 30, 33)$ of one deformation of each model):

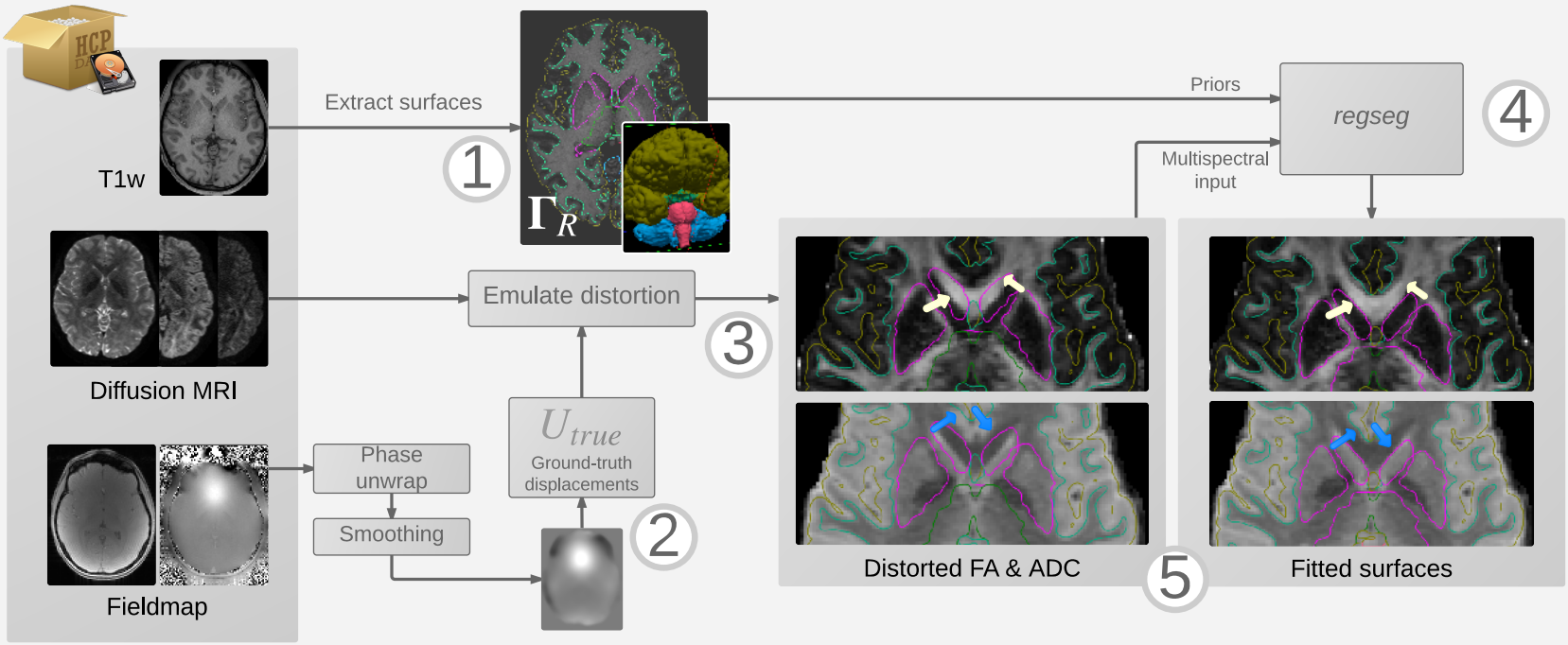


Validating regseg on phantoms (quantitative)

- Registration error measured with **Hausdorff distance** between ground-truth surfaces and those mapped with *regseg*.

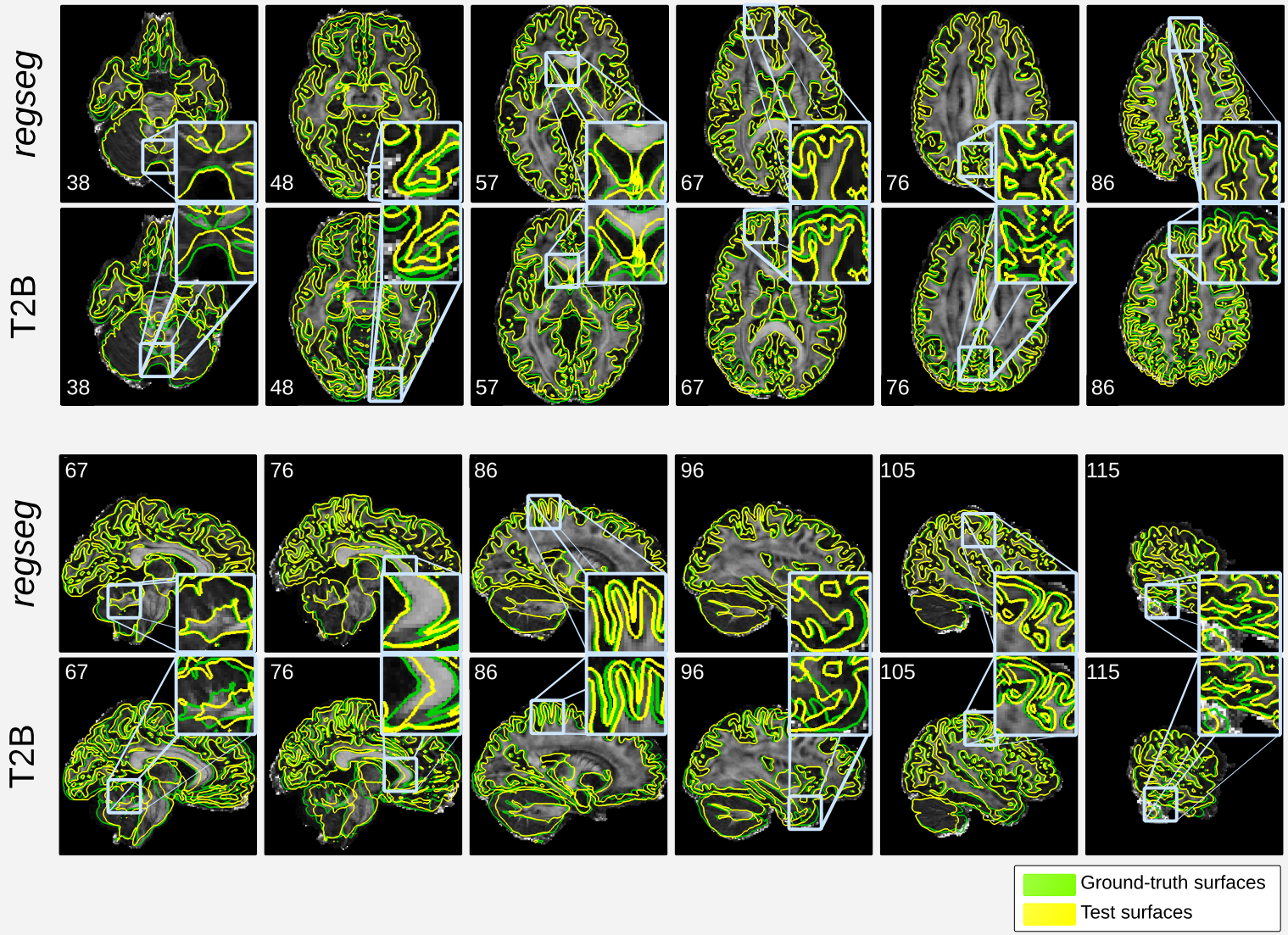


Using regseg on real datasets (methods)



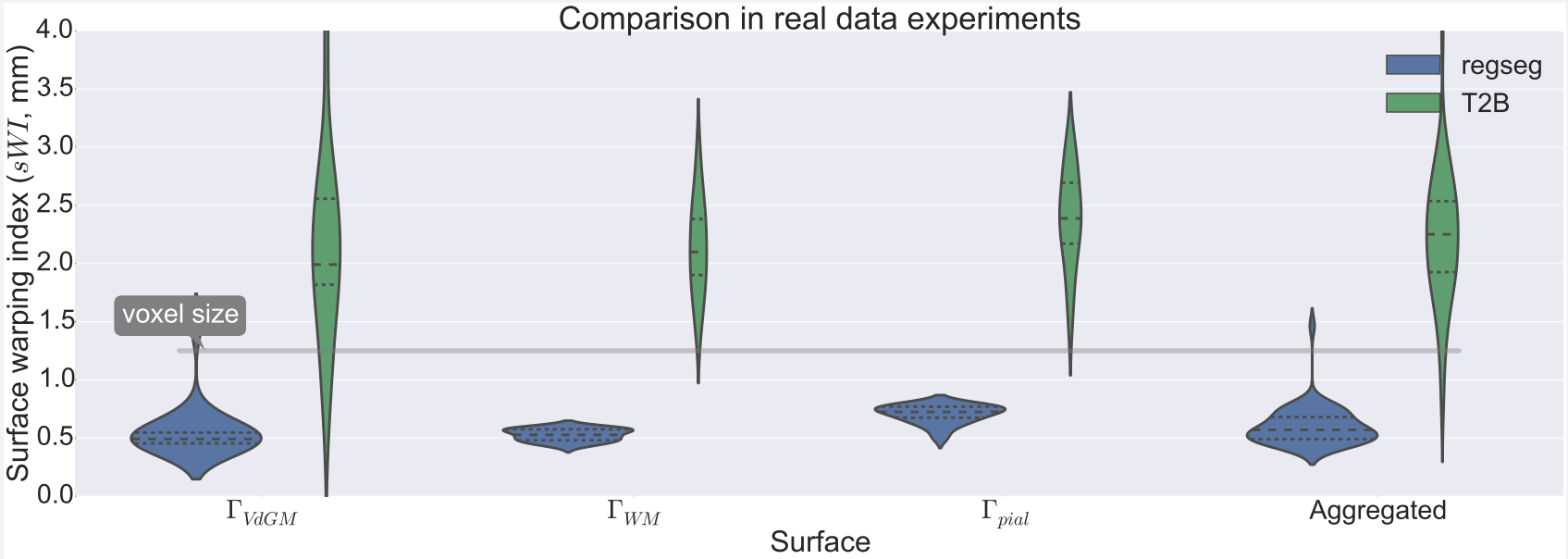
- An equivalent workflow was implemented to run a competing method, a T2-weighted to *b0* registration method (*T2B correction*).
- T2B method configured using *ExploreDTI* (Leemans et al., 2009) settings.
- U_{true} is computed using the fieldmap.

Example report of regseg vs. T2B



Quantitative comparison of regseg vs. T2B

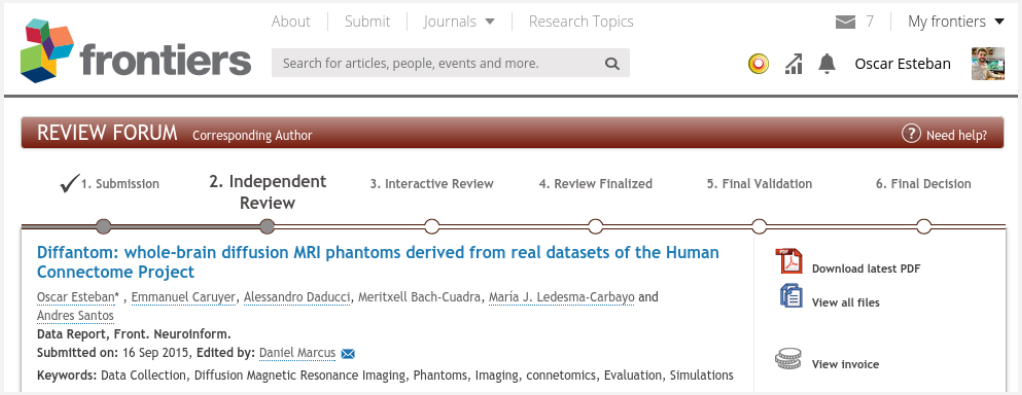
- 16 datasets from the HCP.
- Since displacements happen only in y: evaluated the surface warping index (sWI).
- *regseg* performed significantly better than T2B ($p < 10^{-4}$).



Contributions: whole-brain and ground-truth data

1. *Diffantom*: **a whole-brain dMRI phantom** derived from real datasets, designed for the assessment of processing tasks and full connectivity pipelines.

- We extended *Phantomas*, an existing software to generate dMRI phantoms with analytical fiber geometries, to produce whole-brain data.
- We defined an underlying microstructural model to simulate dMRI phantoms using the hindered and restricted diffusion model of *Phantomas*.
- We publicly release the first *Diffantom*, along with the *diffantomizer* that is the workflow to generate *diffantoms* from HCP datasets.
- Open-sourced.



Contributions: an evaluation framework

2. *PySDCev*: **a comprehensive evaluation framework** for the investigation of susceptibility-derived distortions and the comparison of retrospective correction methods.

- We demonstrated the impact of susceptibility distortion on brain networks.
- We assessed the accurate performance of three SDC methods recovering the distorted anatomy on dMRI images.
- We demonstrated the importance of working on native dMRI space.
- Partially open-sourced, awaiting publication.

Contributions: regseg applied in diffusion MRI

3. We propose *regseg*: **a nonlinear, surface-to-image registration method based on active contours without edges**. The method successfully maps a number of closed surfaces implemented explicitly with 3D meshes into a target image.

- Verified on phantoms.
- Applied on dMRI datasets.
- Sub-voxel accuracy.
- Open-sourced.

New Results

Surface-driven registration method for the structure-informed segmentation of diffusion MR images

Oscar Esteban, Dominique Zosso, Alessandro Daducci, Meritxell Bach-Cuadra, Maria J. Ledesma-Carbayo, Jean-Philippe Thiran, Andres Santos

doi: http://dx.doi.org/10.1101/018945

Abstract Info/History **Metrics** Preview PDF

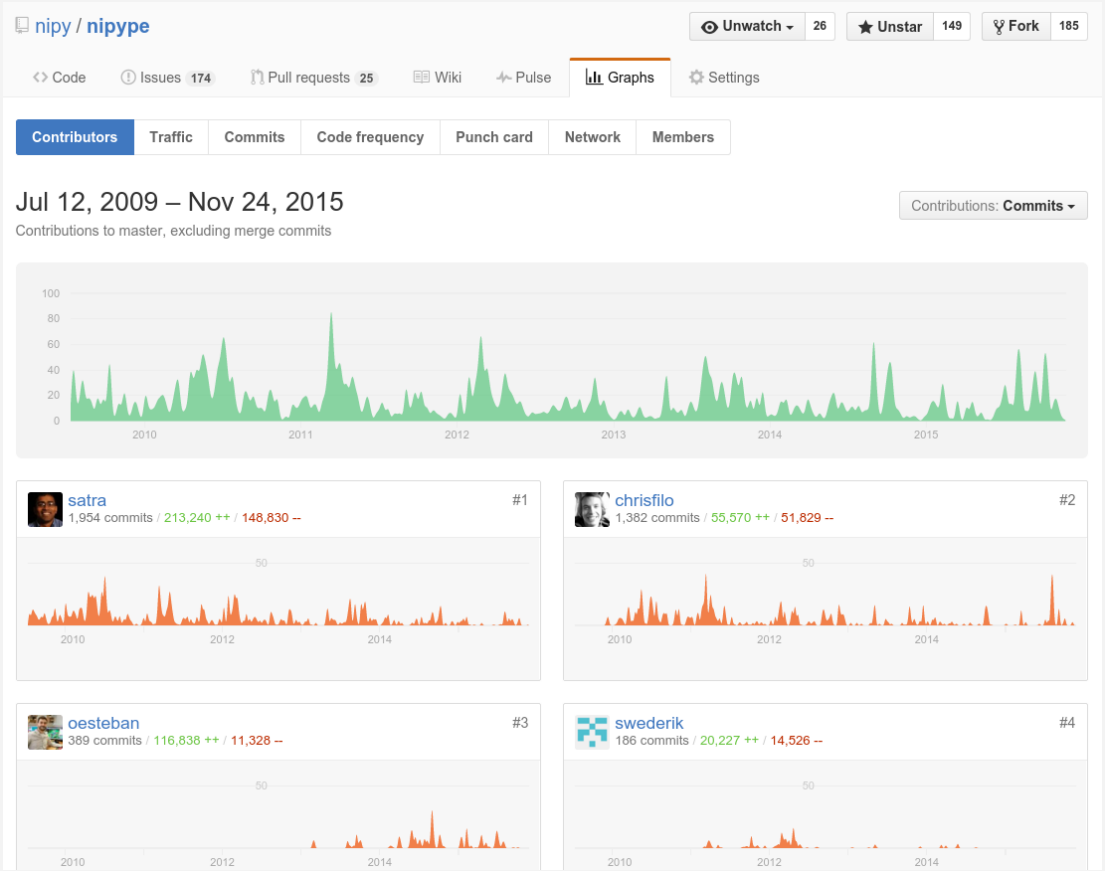
ARTICLE USAGE

Show by month	Abstract	PDF
Total	764	179

- Suitable in applications where we have **precise surfaces** of structures that need be fitted into **multivariate data** and the underlying deformation encodes some **important information** (development, evolution of pathology, etc.)

Contributions: pipelines and experimental instrumentation

4. Important contributions to third-party and open-source tools for dMRI data processing and pipelining of neuroimage processing tools.



Future lines

- **Implementing a new segmentation model working directly on the DWIs for *regseg*.** A recent method proposed by Jeurissen, Tournier, and Sijbers, 2015 uses non-negative matrix factorization of multi-shell dMRI data for tissue-type segmentation.

- **Integrating *regseg* in *PySDCev*.** Currently, *PySDCev* is designed to evaluate SDCs on the undistorted reference grid.

- **Generating a larger sample of *diffantoms*.** With the *Diffantom* presented in this dissertation, only one-subject experiments can be performed with *PySDCev*. This is an important limitation easily solvable with computing capacity, since each *Diffantom* takes around 12 days in an 8-core Intel® Xeon® CPU E31245 @ 3.30GHz, 32GB RAM.

- **Enlarging the number of network metrics tested by *PySDCev*.** Even though we tested the distortion impact on the network densities and the average of clustering coefficients, many more network measures (Duda, Cook, and Gee, 2014) should be included into *PySDCev*, for a better understanding of the confounding factors introduced with distortion.

Publications supporting this Ph.D. Thesis

- Esteban O., Caruyer E., Daducci A., Bach-Cuadra M., Ledesma-Carbayo M.-J., Santos A., *Diffantom: whole-brain diffusion MRI phantoms derived from real datasets of the Human Connectome Project*, Front. Neuroinf. (in revision), 2015. doi:10.1101/026898. (**Ch. 4**)
- Esteban O., Daducci A., Bach-Cuadra M., Ledesma-Carbayo M.-J., Santos A., *PySDCev: A framework to evaluate retrospective correction methods of susceptibility distortion in diffusion MRI*, Magn Res Med (in preparation), 2015. (**Ch. 5**)
- Esteban O., Zosso D., Daducci A., Bach-Cuadra M., Ledesma-Carbayo M.-J., Thiran J.-P., Santos A., *Surface-driven registration method for the structure-informed segmentation of diffusion MR images*, NeuroImage (in revision), 2015. doi:10.1101/018945. (**Ch. 6**)
- Esteban O., Wollny G., Gorthi S., Ledesma-Carbayo M.-J., Thiran J.-P., Santos A., Bach-Cuadra M., *MBIS: Multivariate Bayesian Image Segmentation Tool*, Comp Meth Prog Biomed 115(2):76–95. 2014. doi:10.1016/j.cmpb.2014.03.003. (**Ch. 6**)
- Esteban O., Daducci A., Caruyer E., O'Brien K., Ledesma-Carbayo M.-J., Bach-Cuadra M., Santos A., *Simulation-based evaluation of susceptibility distortion correction methods in diffusion MRI for connectivity analysis*, in 11th ISBI, Beijing, China. 2014. doi:10.1109/ISBI.2014.6867976. (**Ch. 3**)
- Martí-Fuster, Esteban O., Thielemans K., Setoain X., Santos A., Ros D., Pavia J., *Including anatomical and functional information in MC simulation of PET and SPECT brain studies. Brain-VISET: a voxel-based iterative method.*, IEEE Trans Med Imag 33(10):1931–1938. 2014. doi:10.1109/TMI.2014.2326041.
- Bach-Cuadra M., Gelin S., Roche A., Esteban O., Kober T., Marques J., Granziera C., Kreger G., *Classical Segmentation Methods on Novel MR Imaging: A Study of Brain Tissue Segmentation of MP2RAGE Vs MPRAGE*, in 21th ISMRM, p. 948, Salt Lake City, US. 2013.
- Martí-Fuster, Esteban O., Planes X., Aguiar P., Crespo C., Falcon C., Wollny G., Rubí S., Setoain X., Franji F., Ledesma-Carbayo M.-J., Santos A., Pavia J., Ros D., *FocusDET, A New Toolbox for SISCOM Analysis. Evaluation of the Registration Accuracy Using Monte Carlo Simulation*, Neuroinf. 11(1):77–89. 2013. doi:10.1007/s12021-012-9158-x.
- Kober T., Roche A., Esteban O., Gorthi S., Ribes D., Bach-Cuadra M., Meuli R., Kreger G., *Atlas-free Brain Tissue Segmentation Using a Single T1-weighted MRI Acquisition*, in 20th ISMRM, p. 753, Melbourne, Australia. 2012.

Thanks

POLITÉCNICA

"We engineer the future"

Department of
Electronic Engineering

Image processing methods for human brain connectivity analysis from in-vivo diffusion MRI

Ph.D. Thesis

Esteban Sanz-Dranguet, Oscar

Biomedical Image Technologies (BIT),
Dept. Ing. Electrónica
ETSI Telecomunicación, Universidad Politécnica de Madrid
Advisors: Andrés Santos and María-J Ledesma-Carbayo

November 25th, 2015